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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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☒ *Additional inventors are being named on the 1 separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Ephrin Receptor Modulators and Methods of Use

CORRESPONDENCE ADDRESS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 121 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☒ Other (specify) Return Receipt Postcard

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

FILING FEE AMOUNT ($)

☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 50-1108 — 160

☐ Payment by credit card. Form PTO-2038 is attached.

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____.

Respectfully submitted,

SIGNATURE Brian D Griedel Date 2/13/03

TYPED or PRINTED NAME Brian Griedel REGISTRATION NO. (*If appropriate*) 48,425

TELEPHONE 650.837.8326 Docket Number: EX03-008P

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

PROVISIONAL APPLICATION COVER SHEET
Additional Page

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Docket Number	EX03-008P

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Number 1 of 1

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EPHRIN RECEPTOR MODULATORS AND METHODS OF USE

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Even more specifically, the invention relates to quinazolines which inhibit, regulate and/or modulate ephrin family receptor signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, and methods of using them to treat ephrin-dependent diseases and conditions.

Summary of Related Art

[0002] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0003] Protein kinases are enzymes that catalyze the phosphorylation of proteins, in particular, hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell differentiation and proliferation; i.e., virtually all aspects of cell life in one-way or another depend on protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0005] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the

HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and beta receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994, which is hereby incorporated by reference.

[0006] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference.

[0007] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth, associated with cancer. In addition to cancer altered kinase signaling is implicated in numerous other pathological diseases. These include, but not limited to: immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as artheroscrosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0008] One particularly attractive goal for therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the

treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers. Gleevec is a selective Abl kinase inhibitor.

[0009] Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024). EGF and VEGF receptors are previously described targets for small molecule inhibition.

[0010] The Eph receptors comprise the largest family of receptor tyrosine kinases and are divided into two groups, EphA and EphB, based on their sequence homology. The ligands for the Eph receptors are the ephrins, which are membrane anchored. Ephrin A ligands bind preferentially to EphA receptors whilst ephrin B ligands bind to EphB receptors. Binding of ephrins to Eph receptors causes receptor autophosphorylation and typically requires a cell-cell interaction since both receptor and ligand are membrane bound.

[0011] Overexpression of Eph receptors has been linked to increased cell proliferation in a variety of tumors (Zhou R 1998 Pharmacol Ther. 77, 151-181; Kiyokawa E, Takai S, Tanaka M et al 1994 Cancer Res 54, 3645-3650; Takai N Miyazaki T, Fujisawa K, Nasu K and Miyakawa. 2001 Oncology reports 8, 567-573). The family of Eph receptor tyrosine kinases and their ephrin ligands play important roles in a variety of processes during embryonic development and also in pathological angiogenesis and potentially metastasis. Therefore modulation of Eph receptor kinase activity should provide means to treat or prevent disease states associated with abnormal cell proliferation such as those described above.

[0012] Accordingly, the identification of small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of ephrin receptor kinases is desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and is an object of this invention.

SUMMARY OF THE INVENTION

[0013] In one aspect, the present invention provides compounds for modulating ephrin receptor kinase (from herein denoted "ephrin") activity and methods of treating diseases mediated by ephrin activity utilizing the compounds and pharmaceutical compositions thereof. Diseases mediated by ephrin activity include, but are not limited to, diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth),

programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0014] Inhibitors that are selective for a particular kinase are included in this invention, however, another aspect of the invention are compounds that inhibit, regulate and/or modulate the signal transduction of ephrin receptor tyrosine kinase families, family members, or otherwise related sets of kinases. Such related kinase families may include receptor-type tyrosine kinases of the HER, FLK and insulin subfamilies, which demonstrate similarity in both structure and broad biochemical function. Thus quinazolines of the invention include "spectrum selective" kinase modulators. "Spectrum selective" kinase modulators are defined as quinazolines of the invention that inhibit, regulate and/or modulate signal transduction across various subfamilies of receptor-type tyrosine kinases including those of the ephrin receptor tyrosine kinase subfamily.

[0015] In another aspect, the invention provides methods of screening for modulators of ephrin activity. The methods comprise combining a composition of the invention, ephrin, and at least one candidate agent and determining the effect of the candidate agent on the ephrin activity.

[0016] In yet another aspect, the invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of pharmaceutical compounds and/or compositions of the present invention, including, one or more ephrin enzyme activity modulators as described herein. Such kits can also include, for example, other compounds and/or compositions (e.g., diluents, permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflects approval by the agency of manufacture, use or sale for human administration.

[0017] In still yet another aspect, the invention also provides a diagnostic agent comprising a compound of the invention and, optionally, pharmaceutically acceptable adjuvants and excipients.

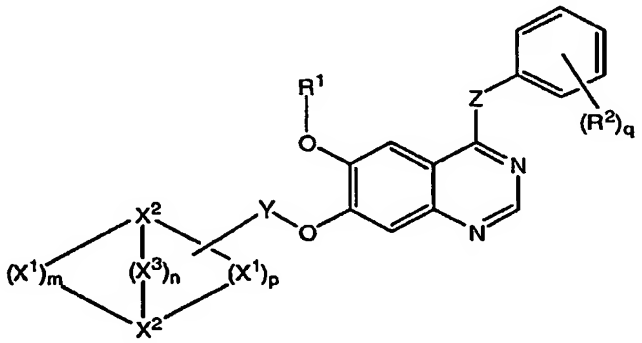
[0018] These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

DETAILED DESCRIPTION OF THE INVENTION

[0019] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as artheroscrosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy.

[0020] It is appreciated that in some cases the cells may not be in a hyper- or hypo-proliferative and/or migratory state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally", but proliferation and migration enhancement may be desired. Alternatively, reduction in "normal" cell proliferation and/or migration rate may be desired.

[0021] The present invention comprises compounds for modulating Ephrin activity of Formula I,



I

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R^1 is an optionally substituted lower alkyl;

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^4$, $-C(O)R^3$, and optionally substituted lower alkyl;

R^3 is -H or R^4;

R^4 is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

R^3 and R^4, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl ring, said optionally substituted five- to seven-membered heterocyclyl ring optionally containing at least one additional heteroatom selected from N, O, S, and P;

q is 0 to 5;

Z is selected from $-OCH_2-$, -O-, $-S(O)_{0-2}-$, $-N(R^5)CH_2-$, and $-NR^5-$;

R^5 is -H or optionally substituted lower alkyl;

X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system containing up to four heteroatoms represented by any of X^1, X^2, and X^3;

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted lower alkylene linker, between the oxygen at the 7-position of the quinazoline ring system of **I** and either 1) any ring atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between any heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7, and the oxygen at the 7-position of the quinazoline ring system of **I**;

or Y is absent, when Y is absent, said saturated bridged ring system, via a carbon atom thereof, is directly attached to the oxygen at the 7-position of the quinazoline ring system of **I**;

m and p are each independently 1-4;

n is 0-2, when n = 0, then there is a direct bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and an attachment point for either Y or the oxygen at the 7-position of the quinazoline ring system of I; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclic ring, said optionally substituted three- to seven-membered spirocyclic ring optionally containing at least one additional heteroatom selected from N, O, S, and P; and

R^8 is selected from R^3, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$;

with the proviso that when Y is a C_{1-6} alkylene, Z is -NH- or $-N(CH_3)-$, R^1 is a C_{1-6}alkyl optionally substituted in the 2-position by -OH or a C_{1-4}alkoxy group, R^2 is -H or halogen, n = 0, and the atoms, X^1, of one bridge of the saturated bridged ring system, when combined with both bridgehead atoms, X^2, of the saturated bridged ring system, represent:

either a pyrrolidine ring or a piperidine ring, and any atom, X^1 or X^2, of either of said pyrrolidine ring or said piperidine ring is attached to Y, then the other bridge of said saturated bridged ring system cannot be any one of $-OC(O)CH_2-$, $-CH_2OC(O)-$, $-OC(O)CH_2CH_2-$, $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, $-OC(O)CH_2NH-$, $-OC(O)CH_2N(C_{1-4}alkyl)-$, and $-OC(O)CH_2O-$; or

either a piperazine ring or a 4-(C_{1-4}alkyl)-piperazine ring, and any atom, X^1 or X^2, of either of said piperazine ring or said 4-(C_{1-4}alkyl)-piperazine ring is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 2- and the 3-position of either of said piperazine

ring or said 4-(C_{1-4}alkyl)-piperazine ring, cannot be one of $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups; or

a piperazine ring, and any atom, X^1 or X^2, of said piperazine ring is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 3- and the 4-position of said piperazine ring, cannot be one of $-C(O)OCH_2CH_2-$, $-CH_2OC(O)CH_2-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups, and only when either of the two aforementioned bridges are attached to the 3-position of said piperazine ring via their left-hand end as depicted above; or

a 2-oxomorpholine ring, said 2-oxomorpholine ring attached to Y via its 4-position, then the other bridge of said saturated bridged ring system, only when attached via the 5- and the 6-position of said 2-oxomorpholine ring, cannot be one of $-(CH_2)_g-$, $-CH_2WCH_2-$, $-CH_2WCH_2CH_2-$, and $-CH_2CH_2WCH_2-$, wherein W is -O-, $-S(O)_{0-2}-$, -NH-, or $-N(C_{1-4}alkyl)-$ wherein g is 2, 3, or 4.

[0022] In one example, the compounds are according to paragraph [0021], wherein Z is $-NR^5-$.

[0023] In another example, the compounds are according to paragraph [0022], wherein R^2 is halogen.

[0024] In another example, the compounds are according to paragraph [0023], wherein R^1 is an unsubstituted lower alkyl.

[0025] In another example, the compounds are according to paragraph [0024], wherein the saturated bridged ring system has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

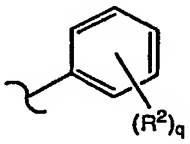
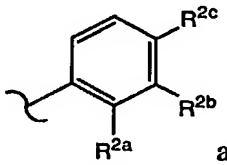
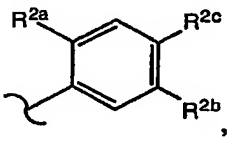
[0026] In another example, the compounds are according to paragraph [0025], wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

[0027] In another example, the compounds are according to paragraph [0026], wherein n = 0 and the saturated bridged ring system has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

[0028] In another example, the compounds are according to paragraph [0027], wherein Y is either $-CH_2-$ or absent.

[0029] In another example, the compounds are according to paragraph [0028], wherein said saturated bridged ring system contains only one ring heteroatom, and said only one ring heteroatom is either $-NR^8-$, when X^1, or a bridgehead nitrogen, when X^2.

[0030] In another example, the compounds are according to paragraph [0029], wherein q = 3.

[0031] In another example, the compounds are according to paragraph [0030], wherein  of **I** is selected from:  and  , wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

[0032] In another example, the compounds are according to paragraph [0031], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

[0033] In another example, the compounds are according to paragraph [0032], wherein R^5 is -H.

[0034] In another example, the compounds are according to paragraph [0033], wherein R^1 is methyl.

[0035] In another example, the compounds are according to paragraph [0034], wherein said only one ring heteroatom is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

[0036] In another example, the compounds are according to paragraph [0035], wherein the remainder of atoms, X^1 and X^2, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are -H, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

[0037] In another example, the compounds are according to paragraph [0034], wherein said only one ring heteroatom is a bridgehead nitrogen, wherein the remainder of atoms, X^1 and X^2, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are either -H or unsubstituted lower alkyl, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

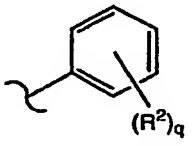
[0038] In another example, the compounds are according to paragraph [0026], wherein n = 1 and the saturated bridged ring system has a geometry selected from the group consisting of [3.3.1], [3.2.1], and [2.2.1].

[0039] In another example, the compounds are according to paragraph [0038], wherein Y is either $-CH_2-$ or absent.

[0040] In another example, the compounds are according to paragraph [0039], wherein said saturated bridged ring system contains only one ring heteroatom, and said only one ring heteroatom is either $-NR^8-$, when X^1 or X^3, or a bridgehead nitrogen, when X^2.

[0041] In another example, the compounds are according to paragraph [0040], wherein q = 3.

[0042] In another example, the compounds are according to paragraph [0041], wherein



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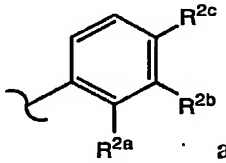
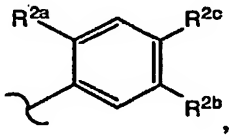


and



, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

[0043] In another example, the compounds are according to paragraph [0042], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

[0044] In another example, the compounds are according to paragraph [0043], wherein R^5 is -H.

[0045] In another example, the compounds are according to paragraph [0044], wherein R^1 is methyl.

[0046] In another example, the compounds are according to paragraph [0045], wherein said only one ring heteroatom is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

[0047] In another example, the compounds are according to paragraph [0046], wherein the remainder of atoms, X^1, X^2, and X^3, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are -H, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

[0048] In another example, the compounds are according to paragraph [0045], wherein said only one ring heteroatom is a bridgehead nitrogen, wherein the remainder of atoms, X^1, X^2, and X^3, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are either -H or unsubstituted lower alkyl, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

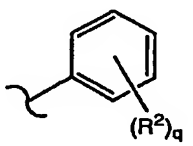
[0049] In another example, the compounds are according to paragraph [0026], wherein n = 2 and the saturated bridged ring system has a geometry selected from the group consisting of [3.3.2], [3.2.2], and [2.2.2].

[0050] In another example, the compounds are according to paragraph [0049], wherein Y is either $-CH_2-$ or absent.

[0051] In another example, the compounds are according to paragraph [0050], wherein said saturated bridged ring system contains only one ring heteroatom, and said only one ring heteroatom is either $-NR^8-$, when X^1 or X^3, or a bridgehead nitrogen, when X^2.

[0052] In another example, the compounds are according to paragraph [0051], wherein q = 3.

[0053] In another example, the compounds are according to paragraph [0052], wherein



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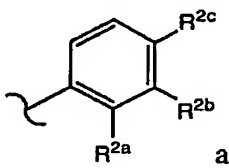

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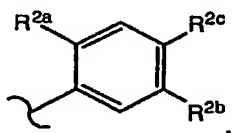


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

[0054] In another example, the compounds are according to paragraph [0053], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

[0055] In another example, the compounds are according to paragraph [0054], wherein R^5 is -H.

[0056] In another example, the compounds are according to paragraph [0055], wherein R^1 is methyl.

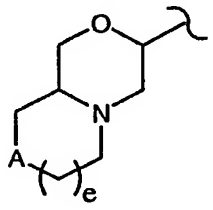
[0057] In another example, the compounds are according to paragraph [0056], wherein said only one ring heteroatom is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

[0058] In another example, the compounds are according to paragraph [0057], wherein the remainder of atoms, X^1, X^2, and X^3, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are -H, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

[0059] In another example, the compounds are according to paragraph [0055], wherein said only one ring heteroatom is a bridgehead nitrogen, wherein the remainder of atoms, X^1, X^2, and X^3, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are either -H or unsubstituted lower alkyl, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

[0060] In another example, the compounds are according to paragraph [0026], wherein Y is selected from $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, and $-CH_2-$.

[0061] In another example, the compounds are according to paragraph [0060], wherein said saturated bridged ring system is of formula **II**



II

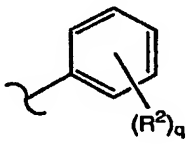
wherein A is selected from -O-, -$S(O)_{0-2}$-, -NR^8-, and absent and e is 0 or 1.

[0062] In another example, the compounds of are according to paragraph [0061], wherein Y is -CH_2-.

[0063] In another example, the compounds are according to paragraph [0062], wherein A is -NR^8-, wherein R^8 is selected from -H, optionally substituted lower alkyl, -CO_2R^4, -$C(O)NR^3R^4$, -SO_2R^4, and -$C(O)R^3$.

[0064] In another example, the compounds are according to paragraph [0063], wherein q = 3.

[0065] In another example, the compounds are according to paragraph [0064], wherein



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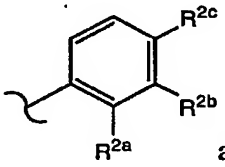

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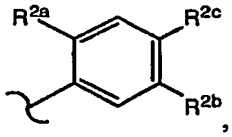


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

[0066] In another example, the compounds are according to paragraph [0065], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

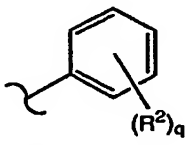
[0067] In another example, the compounds are according to paragraph [0066], wherein R^5 is -H.

[0068] In another example, the compounds are according to paragraph [0067], wherein R^1 is methyl.

[0069] In another example, the compounds are according to paragraph [0062], wherein A is -O-.

[0070] In another example, the compounds are according to paragraph [0069], wherein q = 3.

[0071] In another example, the compounds are according to paragraph [0070], wherein



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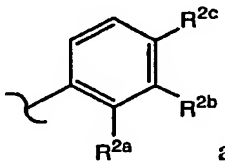

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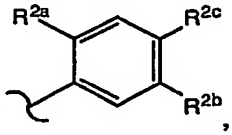


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

[0072] In another example, the compounds are according to paragraph [0071], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

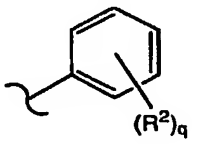
[0073] In another example, the compounds are according to paragraph [0072], wherein R^5 is -H.

[0074] In another example, the compounds are according to paragraph [0073], wherein R^1 is methyl.

[0075] In another example, the compounds are according to paragraph [0062], wherein A is absent.

[0076] In another example, the compounds are according to paragraph [0075], wherein q = 3.

[0077] In another example, the compounds are according to paragraph [0076], wherein



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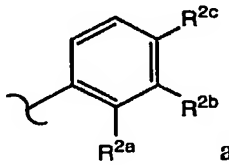

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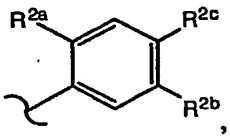


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

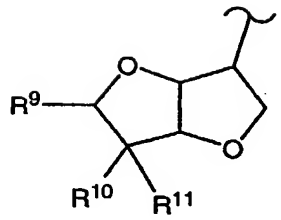
[0078] In another example, the compounds are according to paragraph [0077], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

[0079] In another example, the compounds are according to paragraph [0078], wherein R^5 is -H.

[0080] In another example, the compounds are according to paragraph [0079], wherein R^1 is methyl.

[0081] In another example, the compounds are according to paragraph [0026], wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

[0082] In another example, the compounds are according to paragraph [0081], wherein said saturated bridged ring system is of formula **III**



III

wherein R^9, R^{10}, and R^{11} are each independently selected from -H, and $-OR^{12}$; or

R^9 is selected from -H, and $-OR^{12}$, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo;

R^{12} is selected from -H, $-C(O)R^4$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

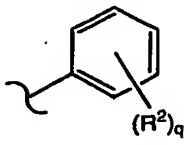
[0083] In another example, the compounds of are according to paragraph [0082], wherein one of R^{10} and R^{11} is $-OR^{12}$, wherein R^{12} is selected from -H, $-C(O)R^4$, and optionally substituted lower alkyl; and R^9 and the other of R^{10} and R^{11} are both -H.

[0084] In another example, the compounds of are according to paragraph [0083], wherein Y is either $-CH_2-$ or absent.

[0085] In another example, the compounds of are according to paragraph [0083], wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

[0086] In another example, the compounds are according to paragraph [0084], wherein $q = 3$.

[0087] In another example, the compounds are according to paragraph [0085], wherein



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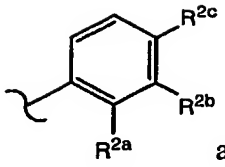

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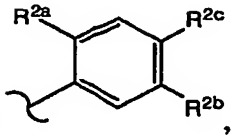


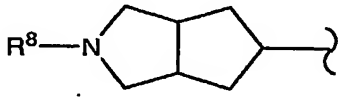
, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

[0088] In another example, the compounds are according to paragraph [0087], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

[0089] In another example, the compounds are according to paragraph [0088], wherein R^5 is -H.

[0090] In another example, the compounds are according to paragraph [0089], wherein R^1 is methyl.

[0091] In another example, the compounds are according to paragraph [0081], wherein said saturated bridged ring system is of formula **IV**



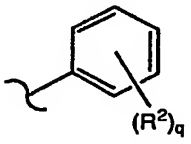
IV

wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

[0092] In another example, the compounds of are according to paragraph [0091], wherein Y is either $-CH_2-$ or absent.

[0093] In another example, the compounds are according to paragraph [0092], wherein q = 3.

[0094] In another example, the compounds are according to paragraph [0093], wherein



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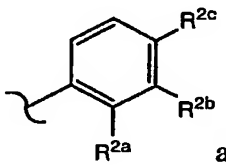

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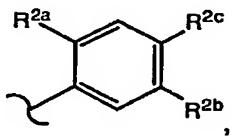


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

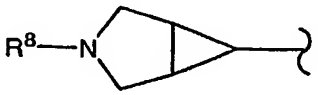
[0095] In another example, the compounds are according to paragraph [0094], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

[0096] In another example, the compounds are according to paragraph [0095], wherein R^5 is -H.

[0097] In another example, the compounds are according to paragraph [0096], wherein R^1 is methyl.

[0098] In another example, the compounds are according to paragraph [0097], wherein R^8 is methyl.

[0099] In another example, the compounds are according to paragraph [0081], wherein said saturated bridged ring system is of formula V



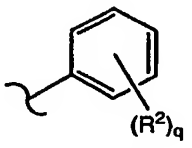
V

wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

[0100] In another example, the compounds of are according to paragraph [0099], wherein Y is $-CH_2-$.

[0101] In another example, the compounds are according to paragraph [0100], wherein q = 3.

[0102] In another example, the compounds are according to paragraph [0101], wherein



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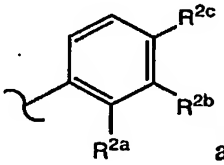

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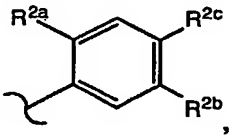


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

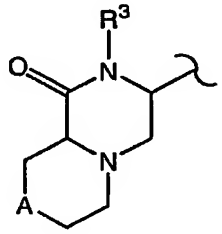
[0103] In another example, the compounds are according to paragraph [0102], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

[0104] In another example, the compounds are according to paragraph [0103], wherein R^5 is -H.

[0105] In another example, the compounds are according to paragraph [0104], wherein R^1 is methyl.

[0106] In another example, the compounds are according to paragraph [0105], wherein R^8 is methyl.

[0107] In another example, the compounds are according to paragraph [0081], wherein said saturated bridged ring system is of formula **VI**



VI

wherein A is selected from -O-, -$S(O)_{0-2}$-, -NR^8-, -CR^6R^7-, and absent.

[0108] In another example, the compounds are according to paragraph [0107], wherein R^3 is selected from -H and optionally substituted alkyl.

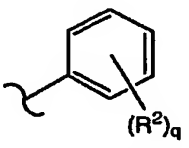
[0109] In another example, the compounds are according to paragraph [0108], wherein A is either -CR^6R^7- or absent.

[0110] In another example, the compounds are according to paragraph [0109], wherein A is either -CH_2- or absent.

[0111] In another example, the compounds of are according to paragraph [0110], wherein Y is -CH_2-.

[0112] In another example, the compounds are according to paragraph [0111], wherein q = 3.

[0113] In another example, the compounds are according to paragraph [0112], wherein



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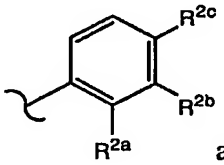

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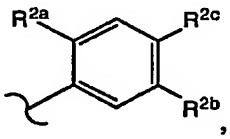


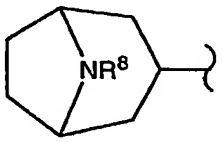
, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

[0114] In another example, the compounds are according to paragraph [0113], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

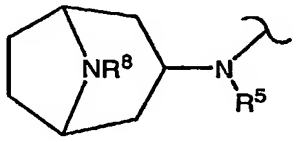
[0115] In another example, the compounds are according to paragraph [0114], wherein R^5 is -H.

[0116] In another example, the compounds are according to paragraph [0115], wherein R^1 is methyl.

[0117] In another example, are according to paragraph [0081], wherein Y is $-CH_2CH_2-$ and said saturated bridged ring system is chosen from either of formula **VII** or **VIII**



VII

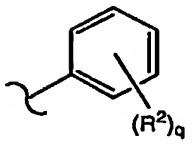


VIII

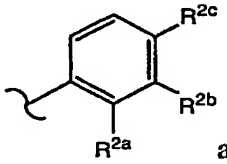
wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

[0118] In another example, are according to paragraph [0117], wherein q = 3.

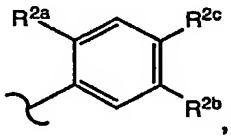
[0119] In another example, are according to paragraph [0118], wherein



of **I** is selected from:



and



, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

[0120] In another example, are according to paragraph [0119], wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or BrThe compound according to claim 100, wherein R^5 is -H.

[0121] In another example, are according to paragraph [0120], wherein R^1 is methyl.

[0122] In another example, are according to paragraph [0121], wherein R^8 is methyl.

[0123] In another example, the compounds are according to paragraph [0021], selected from the compounds in Table 1.

Table 1

#	Name

#	Name
1	N-(3,4-dichloro-2-fluorophenyl)-7-({[(3aR,5r,6aS)-2-(1-methylethyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
2	N-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3aR,5r,6aS)-2-(1-methylethyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
3	7-({[(3aR,5r,6aS)-2-acetyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-N-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)quinazolin-4-amine
4	N-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3aR,5r,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine
5	ethyl (3aR,6aS)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate
6	N-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3aR,5r,6aS)-2-(methylsulfonyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
7	N-(3,4-dichloro-2-fluorophenyl)-7-({[(3aR,5r,6aS)-2-ethyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
8	N-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3aR,5r,6aS)-2-(2-methylpropyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
9	N-(3,4-dichloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
10	N-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
11	N-(3-chloro-2,4-difluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
12	N-(4,5-dichloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
13	N-(4-bromo-5-chloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
14	N-(4-bromo-2,3-dichlorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
15	N-(3,4-dichlorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
16	N-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3aR,5r,6aS)-2-ethyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine

#	Name
17	N-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3aR,5r,6aS)-2-(2-methylpropyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
18	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
19	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
20	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
21	N-(3-chloro-2,4-difluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
22	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
23	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
24	N-(3-chloro-2,4-difluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
25	N-(3,4-dichlorophenyl)-7-[(hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl)oxy]-6-(methyloxy)quinazolin-4-amine
26	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
27	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
28	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
29	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
30	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
31	N-(3,4-dichlorophenyl)-7-{[(3R,8aR)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
32	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine

#	Name
33	N-(3,4-dichlorophenyl)-7-{[(3S,8aR)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
34	N-(3,4-dichlorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
35	N-(3,4-dichlorophenyl)-7-{[(3R,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
36	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
37	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
38	N-(3-chloro-2,4-difluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
39	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
40	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
41	1,4:3,6-dianhydro-5-({[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
42	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-glucitol
43	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-xylo-hexitol
44	1,4:3,6-dianhydro-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
45	1,4:3,6-dianhydro-5-({[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
46	1,4:3,6-dianhydro-5-({[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-glucitol
47	1,4:3,6-dianhydro-2-deoxy-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-O-methyl-D-threo-hexitol
48	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-glucitol

#	Name
49	(3S,9aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one
50	(3S,9aR)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one
51	(3S,8aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one
52	(3S,8aR)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one
53	(3S,8aS)-3-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one
54	(3S,8aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one
55	N-(3,4-dichlorophenyl)-7-({2-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]ethyl}oxy)-6-(methyloxy)quinazolin-4-amine
56	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(8aR)-tetrahydro-1H-[1,3]thiazolo[4,3-c][1,4]oxazin-6-ylmethyl]oxy}quinazolin-4-amine
57	N-(3,4-dichlorophenyl)-7-{[2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ethyl]oxy}-6-(methyloxy)quinazolin-4-amine
58	N-(3,4-dichlorophenyl)-7-{[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
59	N-(3,4-dichlorophenyl)-7-{[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]oxy}-6-(methyloxy)quinazolin-4-amine
60	N-(3,4-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-6-(methyloxy)quinazolin-4-amine
61	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
62	1,4:3,6-dianhydro-2-O-[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
63	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
64	1,4:3,6-dianhydro-2-O-methyl-5-O-{6-(methyloxy)-4-[(2,3,4-trichlorophenyl)amino]quinazolin-7-yl}-L-iditol

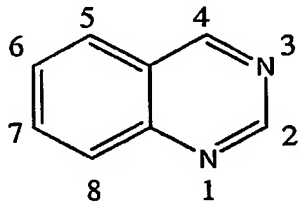
#	Name
65	1,4:3,6-dianhydro-5-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-D-xylo-hexitol
66	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
67	dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-sorbose ethylene glycol acetal
68	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
69	1,4:3,6-dianhydro-2-O-[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
70	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-(difluoromethyl)-L-iditol
71	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
72	1,4:3,6-dianhydro-2-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
73	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
74	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-ethyl-L-iditol
75	1,4:3,6-dianhydro-2-O-[4-[(3-bromo-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
76	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
77	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-D-xylo-hexitol
78	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-D-glucitol
79	methyl 3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-alpha-L-idofuranoside
80	3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-1,2-O-(1-methylethylidene)-beta-L-xylo-hexofuranose

#	Name
81	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-5-methylidene-D-xylo-hexitol
82	methyl 3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-beta-L-idofuranoside
83	N-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-[(octahydro-2H-quinolizin-3-ylmethyl)oxy]quinazolin-4-amine

Definitions

[0124] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

[0125] The atom numbering convention for the quinazoline structure is as follows:



[0126] "Alkyl" is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, "C_8 alkyl" may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to eight carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more that 6 carbon atoms. Exemplary alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 13 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus either "butyl" or "C_4alkyl" is meant to include n-butyl, sec-butyl, isobutyl, t-butyl,

isobutenyl and but-2-yne radicals, for example; "propyl" or "C_3alkyl" each include n-propyl, propenyl, and isopropyl, for example.

[0127] "Alkylene" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, e.g., methylene, ethylene, propylene, n-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and specifically fully saturated. Examples of alkylene include ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), dimethylpropylene ($-CH_2C(CH_3)_2CH_2-$) and cyclohexylpropylene ($-CH_2CH_2CH(C_6H_{13})$).

[0128] "Alkylidene" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, e.g., ethylidene, propylidene, n-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and specifically double bond unsaturation. The unsaturation present includes at least one double bond and a double bond can exist between the first carbon of the chain and a carbon atom of the rest of the molecule to which it is attached.

[0129] "Alkylidyne" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, e.g., propylid-2-ynyl, n-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and specifically triple bond unsaturation. The unsaturation present includes at least one triple bond and a triple bond can exist between the first carbon of the chain and a carbon atom of the rest of the molecule to which it is attached.

[0130] Any of the above radicals, "alkylene," "alkylidene" and "alkylidyne," when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an n-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

[0131] "Alkoxy" or "alkoxyl" refers to the group -O-alkyl, for example including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen. Examples include

methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0132] "Substituted alkoxy" refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O- (optionally substituted alkylene)-(optionally substituted alkoxy), and includes groups such as $-OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and $-O(CH_2CH_2O)_xCH_3$, where x is an integer of between about 2 and about 20, in another example, between about 2 and about 10, and in a further example between about 2 and about 5. Another exemplary substituted alkoxy group is hydroxyalkoxy or $-OCH_2(CH_2)_yOH$, where y is for example an integer of between about 1 and about 10, in another example y is an integer of between about 1 and about 4.

[0133] "Acyl" refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, t-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0134] "α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α-amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, omithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

[0135] "Amino" refers to the group $-NH_2$. "Substituted amino," refers to the group -NHR or -NRR where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl,

acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, e.g., diethylamino, methylsulfonylamino, furanyl-oxy-sulfonamino.

[0136] "Aryl" refers to aromatic 6- to 14-membered carbocyclic rings include, e.g., benzene, naphthalene, indane, tetralin, fluorene and the like.

[0137] "Arylalkyl" refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. The aryl, alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower arylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to eight carbons.

[0138] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine. Dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0139] "Heteroatom" refers to O, S, N, or P.

[0140] "Heterocyclyl" refers to a stable 3- to 15-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems, and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of such heterocyclyl ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl,

morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0141] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl ring system radical.

[0142] "Heteroaryl" refers specifically to an aromatic heterocyclyl ring system radical.

[0143] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl ring is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. The heterocyclyl, alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower heterocyclylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to eight carbons.

[0144] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*) that are sterically impractical and/or synthetically non-feasible. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted C_{1-8}alkylaryl," optional substitution may occur on both the "C_{1-8}alkyl" portion and the "aryl" portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*. Examples of optional substitution include, but are not limited to alkyl, halogen, alkoxy, hydroxy, oxo, carbamyl, acylamino, sulfonamido, carboxy,

alkoxycarbonyl, acyl, alkylthio, alkylsulfonyl, nitro, cyano, amino, alkylamino, cycloalkyl and the like.

[0145] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, 2,3,3a,4,7,7a-hexahydro-1H-indene and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are included in the class "saturated bridged ring system."

[0146] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about 5, in another example, up to about 3) hydrogen atoms are replaced by a substituent independently selected from the group: optionally substituted alkyl (e.g., fluoroalkyl), optionally substituted alkoxy, alkylenedioxy (e.g. methylenedioxy), optionally substituted amino (e.g., alkylamino and dialkylamino), optionally substituted amidino, optionally substituted aryl (e.g., phenyl), optionally substituted arylalkyl (e.g., benzyl), optionally substituted aryloxy (e.g., phenoxy), optionally substituted arylalkyloxy (e.g., benzyloxy), carboxy (-COOH), carboalkoxy (i.e., acyloxy or -OOCR), carboxyalkyl (i.e., esters or -COOR), carboxamido, aminocarbonyl, benzyloxycarbonylamino (CBZ-amino), cyano, carbonyl, halogen, hydroxy, optionally substituted heterocyclylalkyl, optionally substituted heterocyclyl, nitro, sulfanyl, sulfinyl, sulfonyl, and thio.

[0147] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0148] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

[0149] "Sulfonyl" refers to the groups: $-S(O_2)$-H, $-S(O_2)$-(optionally substituted alkyl), $-S(O_2)$-optionally substituted aryl), $-S(O_2)$-(optionally substituted heterocyclyl), $-S(O_2)$-(optionally substituted alkoxy), $-S(O_2)$-optionally substituted aryloxy), and $-S(O_2)$-(optionally substituted heterocyclyloxy).

[0150] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0151] In some embodiments, as will be appreciated by those in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring

structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) may contain two substitution groups.

[0152] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl ring systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0153] Compounds of the invention are generally named using ACD/Name (available from Advanced Chemistry Development, Inc. of Toronto, Canada). This software derives names from chemical structures according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0154] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0155] The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0156] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one skilled in the art would recognize that there may theoretically be some constructs which would not normally be considered as stable compounds. Stable constructs for the saturated bridged ring system as represented by X^1, X^2, and optionally X^3 of formula **I** include but are not limited to motifs such as: 1) where heteroatoms of a ring or bridge thereon are bonded directly to each other, for example a bridge containing a sulfonamide, 2) where heteroatoms of a ring or bridge thereon are separated by only one carbon, for example a urea, carbamate, acetal, aminal, thioacetal, thioaminal, amidine, guanidine, and the like, 3) where heteroatoms of a ring or bridge

thereon are separated by two or more carbons, for example an $-NHCH_2CH_2O-$ bridge, and the like, and 4) where heteroatoms in the bridged ring system are separated by more than two carbon atoms, for example wherein the bridged ring system is a decahydro-isoquinoline.

[0157] When a particular group with its bonding stucture is denoted as being bonded to two partners, e.g. $-OCH_2-$, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group.

[0158] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When desired, the R- and S- isomers may be resolved by methods known to those skilled in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0159] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond, and "〰" refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached.

[0160] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human

therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0161] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0162] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0163] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0164] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous

hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinorna, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [neplrroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal

cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal lands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0165] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0166] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0167] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable

[redacted]

esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about 1 and about 6 carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about 1 and about 6 carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0168] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; e.g., biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0169] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0170] In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[0171] "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation, and invasion and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

General Administration

[0172] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0173] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0174] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0175] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0176] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0177] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0178] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0179] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0180] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0181] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0182] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0183] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0184] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0185] The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to those skilled in the art.

Utility of compounds of the invention as screening agents

[0186] To employ the compounds of the invention in a method of screening for candidate agents that bind to, for example an ephrin receptor kinase, the protein is bound to a support, and a compound of the invention is added to the assay. Alternatively, the compound of the

invention is bound to the support and the protein is added. Classes of candidate agents among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

[0187] The determination of the binding of the candidate agent to, for example, an ephrin protein may be done in a number of ways. In one example, the candidate agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding determined directly. For example, thus may be done by attaching all or a portion of the ephrin protein to a solid support, adding a labeled agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

[0188] By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

[0189] In some embodiments, only one of the components is labeled. For example, an ephrin protein may be labeled at tyrosine positions using ^{125}I, or with fluorophores. Alternatively, more than one component may be labeled with different labels; using ^{125}I for the proteins, for example, and a fluorophor for the candidate agents.

[0190] The compounds of the invention may also be used as competitors to screen for additional drug candidates. "Candidate bioactive agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity. They may be

capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. In the case where protein binding or activity is screened, some embodiments exclude molecules already known to bind to that particular protein. Exemplary embodiments of assays described herein include candidate agents, which do not bind the target protein in its endogenous native state, termed herein as "exogenous" agents. In one example, exogenous agents further exclude antibodies to ephrins.

[0100] Candidate agents can encompass numerous chemical classes, though typically they are organic molecules having a molecular weight of more than about 100 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclyl structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

[0101] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

[0102] In one example, the binding of the candidate agent is determined through the use of competitive binding assays. In this example, the competitor is a binding moiety known to bind to ephrins, such as an antibody, peptide, binding partner, ligand, etc. Under certain

circumstances, there may be competitive binding as between the candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

[0103] In some embodiments, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to an ephrin for a time sufficient to allow binding, if present. Incubations may be performed at any temperature that facilitates optimal activity, typically between 4°C and 40°C.

[0104] Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0105] In one example, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to an ephrin and thus is capable of binding to, and potentially modulating, the activity of the ephrin. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

[0106] In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to an ephrin with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to an ephrin.

[0107] It may be of value to identify the binding site of an ephrin. This can be done in a variety of ways. In one embodiment, once an ephrin has been identified as binding to the candidate agent, the ephrin is fragmented or modified and the assays repeated to identify the necessary components for binding.

[0108] Modulation is tested by screening for candidate agents capable of modulating the activity of ephrins comprising the steps of combining a candidate agent with an ephrin, as above, and determining an alteration in the biological activity of the ephrin. Thus, in this embodiment, the candidate agent should both bind to (although this may not be necessary),

and alter its biological or biochemical activity as defined herein. The methods include both *in vitro* screening methods and *in vivo* screening of cells for alterations in cell viability, morphorlogy, and the like.

[0109] Alternatively, differential screening may be used to identify drug candidates that bind to native ephrins, but cannot bind to modified ephrins.

[0110] Positive controls and negative controls may be used in the assays. For example, all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples may be counted in a scintillation counter to determine the amount of bound compound.

[0111] A variety of other reagents may be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components may be added in any order that provides for the requisite binding.

[0112] Abbreviations and their Definitions

The following abbreviations and terms have the indicated meanings throughout:

Ac	=	acetyl
ATP	=	adenosine triphosphate
BNB	=	4-bromomethyl-3-nitrobenzoic acid
Boc	=	t-butyloxy carbonyl
br	=	broad
Bu	=	butyl
C	=	degrees Celsius
c-	=	cyclo
CBZ	=	carbobenzoxy = benzyloxycarbonyl
d	=	doublet
dd	=	doublet of doublet
dt	=	doublet of triplet

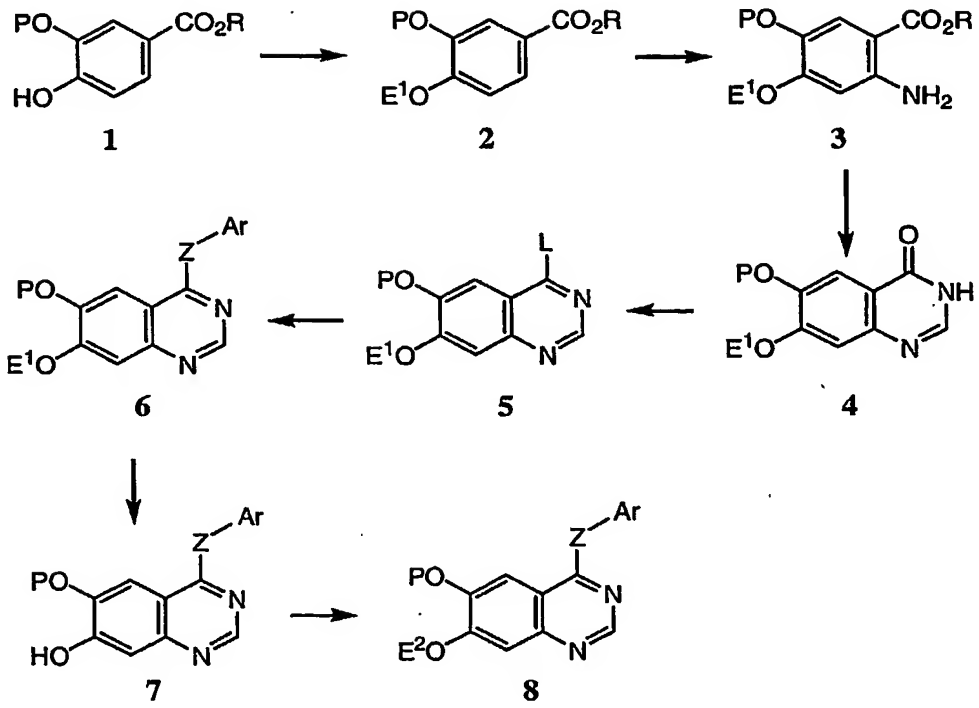
DBU	=	diazabicyclo[5.4.0]undec-7-ere
DCM	=	dichloromethane = methylene chloride = CH_2Cl_2
DCE	=	dichloroethylene
DEAD	=	diethyl azodicarboxylate
DIC	=	diisopropylcarbodiimide
DIEA	=	N,N-diisopropylethyl amine
DMAP	=	4-N,N-dimethylaminopyridine
DMF	=	N,N-dimethylfonnamide
DMSO	=	dimethyl sulfoxide
DVB	=	1,4-divinylbenzene
EEDQ	=	2-ethoxy-l-ethoxycarbonyl-1,2-dihydroquinoline
EI	=	Electron Impact ionization
Et	=	ethyl
Fmoc	=	9-fluorenylmethoxycarbonyl
g	=	gram(s)
GC	=	gas chromatography
h or hr	=	hour(s)
HATU	=	0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	=	hexamethyldisilazane
HOAc	=	acetic acid
HOBt	=	hydroxybenzotriazole
HPLC	=	high pressure liquid chromatography
L	=	liter(s)
M	=	molar or molarity
m	=	multiplet
Me	=	methyl
mesyl	=	methanesulfonyl
mg	=	milligram(s)
MHz	=	megahertz (frequency)
Min	=	minute(s)
mL	=	milliliter(s)
mM	=	millimolar
mmol	=	millimole(s)
mol	=	mole(s)
MS	=	mass spectral analysis
MTBE	=	methyl t-butyl ether
N	=	normal or normality

NBS	=	N-bromosuccinimide
NCS	=	N-chlorosuccinimide
nM	=	nanomolar
NMO	=	N-methylmorpholine oxide
NMR	=	nuclear magnetic resonance spectroscopy
PEG	=	polyethylene glycol
pEY	=	poly-glutamine, tyrosine
Ph	=	phenyl
PhOH	=	phenol
PfP	=	pentafluorophenol
PfPy	=	pentafluoropyridine
PPTS	=	pyridinium p-toluenesulfonate
Py	=	pyridine
PyBroP	=	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	=	quartet
RT	=	room temperature
Sat'd	=	saturated
s	=	singlet
s-	=	secondary
t-	=	tertiary
t or tr	=	triplet
TBDMS	=	t-butyldimethylsilyl
TES	=	triethylsilane
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TMOF	=	trimethyl orthoformate
TMS	=	trimethylsilyl
tosyl	=	p-toluenesulfonyl
Trt	=	triphenylmethyl
uL	=	microliter(s)
uM	=	micromole(s) or micromolar

[redacted]

Synthesis of Compounds

Scheme 1



[0113] Scheme 1 depicts a general synthetic route for compounds of the invention and is not intended to be limiting. Specific examples are described subsequently to this general synthetic description. A benzoic ester **1**, where R is typically but not necessarily a methyl radical and P is typically but not necessarily an alkyl group, is O-alkylated at the oxygen *para* to the carboxylate group with an electrophile to afford a substituted derivative **2**. P is typically a lower alkyl group, but may be a protecting group that is removed later in a synthesis. When P is a lower alkyl group it may possess functionality initially, or be derivitized to contain such functionality at various stages of the synthesis. The group, E^1, may represent either a protecting group, e.g. benzyl, or a group that either has moieties present in compounds of the invention or possesses functionality that serve as a precursors to such groups. Aromatic ring nitration and reduction of the corresponding nitro group are carried out in a regio- and chemoselective manner by methods well known in the art to give anthranilate derivative **3**. Formation of quinazolin-4-one **4** is carried out by methods well known in the art, for example by heating **3** in formamide solution in the presence of

ammonium formate or for example by heating directly with formamidine hydrochloride. Introduction of 4-position functionality groups is carried out by methods known in the art. For example, quinazolin-4-one **4** is converted to an intermediate quinazoline **5**, where "L" represents a leaving group, e.g. chlorine. Quinazoline **5** is then converted to **6** by reaction with a range of nucleophiles, e.g. amines, alcohols, and thiols. After formation of **6**, group "Z" is either left "as is" or converted at some subsequent stage to a derivative thereof. For example when Z is -NH-, then the hydrogen on the nitrogen may optionally be replaced with an alkyl group, or when Z is sulfur, then that sulfur atom may be oxidized to, for example, a sulfone. Compound **6** may represent a compound of the invention or, for example when E^1 serves as a protecting group, E^1 may be removed to provide phenol **7**. Introduction of a group E^2 is carried out by methods well established in the art; for example alkylation with an appropriately derivatized alkyl halide.

Examples

[0114] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety. Generally, each example set out below describes a multi-step synthesis as outlined above.

Example 1

1,4:3,6-Dianhydro-2-*O*-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol

[0115] 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol: To a solution of 1,4:3,6-dianhydro-2-*O*-methyl-D-glucitol (1.19g, 7.4 mmol) in dichloromethane was added pyridine (1mL, 12.36 mmol) followed by methanesulfonyl chloride (0.69mL, 8.92 mmol) and the mixture was allowed to stir at room temperature over 12 hours. The solvent was removed and the amorphous residue was partitioned with ethyl acetate and 0.1M aqueous hydrochloric acid. The aqueous phase was extracted once with additional ethyl acetate and

the combined organic layers were washed with saturated aqueous sodium chloride then dried over anhydrous magnesium sulfate. Filtration and concentration followed by drying *in vacuo* afforded 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol (1.67g, 94% yield) as a colorless oil. GCMS calculated for $C_8H_{14}SO_6$: 238 (M^+).

[0116] 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol: 4-Chloro-6-(methyloxy)-7-[(phenylmethyl)oxy]quinazoline hydrochloride (22.91g, 67.9 mmol) was suspended in isopropanol followed by addition of 3,4-dichloroaniline (13.2g, 81.5 mmol) and concentrated aqueous hydrochloric acid (1mL). The mixture was brought to reflux over 12 hours and diluted with ethyl ether (150mL). The solid was collected by filtration, washed with additional ethyl ether and dried. The material was then taken into trifluoroacetic acid (150mL) and brought to reflux over 1 hour. The solution was cooled to room temperature then concentrated *in vacuo* to give a crystalline residue. The residue was suspended in acetonitrile (100mL) followed by addition of ethyl ether (100mL). The solid was collected by filtration and washed with additional ethyl ether then dried *in vacuo* to give 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol (21.49g, 64% yield) as a tan solid. ^{1}H NMR (400 MHz, d_6-DMSO): 11.09 (br s, 1H), 8.87 (s, 1H), 8.07 (d, 1H), 8.00 (s, 1H), 7.23 (s, 1H), 3.98 (s, 3H); MS (EI) for $C_{15}H_{11}N_3O_2Cl_2$: 337 (MH^+).

[0117] 1,4:3,6-dianhydro-2-*O*-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol hydrochloride: A suspension of 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol (1.70g, 3.78 mmol), 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol (1.00g, 4.20 mmol), and potassium carbonate (2.64g, 19.10 mmol) in DMF (20mL) was stirred at 80°C under nitrogen for 15 h. The reaction mixture was poured into water (100mL), and extracted with ethyl acetate (3 x 50mL). The organic layers were washed with 5% LiCl (2 x 50mL), and brine (50mL) then dried over anhydrous sodium sulfate. Filtration, concentration and column chromatography on silica (97:3 dichloromethane/methanol) gave a solid, which was dissolved in methanol (50mL), and treated with 4M HCl in 1,4-dioxane (5mL). The resulting precipitation was filtered, washed with methanol (2 x 20mL), and dried to afford 0.99g (51%) of 1,4:3,6-dianhydro-2-*O*-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol hydrochloride as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 11.51 (br s, 1H), 8.91 (s, 1H), 8.38 (s, 1H), 8.16 (d, 1H), 7.82 (dd, 1H), 7.76 (d, 1H), 7.42 (s, 1H), 5.03

(m, 1H), 4.66 (m, 2H), 4.11 (m, 1H), 4.04 (s, 3H), 4.02 (m, 1H), 3.90 (m, 3H), 3.31 (s, 3H); MS (EI) for $C_{22}H_{21}N_3O_5Cl_2$: 478 (MH^+).

[0118] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0119] 1,4:3,6-dianhydro-2-*O*-[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 8.76 (s, 1H), 8.09 (s, 1H), 7.79 (dd, 1H), 7.55 (t, 1H), 7.39 (s, 1H), 5.10-5.06 (m, 1H), 4.65 (s, 2H), 4.11 (dd, 1H), 4.04-4.02 (m, 1H), 4.00 (s, 3H), 3.94-3.91 (m, 1H), 3.90-3.87 (m, 2H), 3.31 (s, 3H); MS (EI) for $C_{22}H_{20}BrClFN_3O_5$: 540 (MH^+).

[0120] 1,4:3,6-dianhydro-2-*O*-[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 8.77 (s, 1H), 8.13 (s, 1H), 7.96 (d, 1H), 7.56 (d, 1H), 7.42 (s, 1H), 5.10-5.06 (m, 1H), 4.66 (s, 2H), 4.12 (dd, 1H), 4.05-4.02 (m, 1H), 4.00 (s, 3H), 3.94-3.91 (m, 1H), 3.90-3.87 (m, 2H), 3.31 (s, 3H); MS (EI) for $C_{22}H_{20}BrCl_2N_3O_5$: 556 (MH^+).

[0121] 1,4:3,6-Dianhydro-2-*O*-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 9.63 (s, 1H), 8.30 (s, 1H), 7.86 (s, 1H), 7.41 (m, 1H), 7.30 (m, 2H), 7.26 (s, 1H), 5.05 (br s, 1H), 4.63 (dd, 2H), 4.03 (ddd AB, 2H), 3.95 (s, 3H), 3.91 (s, 1H), 3.86 (d, 2H), 3.31 (s, 3H), 2.19 (s, 3H); MS (EI) for $C_{23}H_{24}N_3O_5Cl$: 458 (MH^+).

[0122] 1,4:3,6-Dianhydro-2-*O*-[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 9.69 (s, 1H), 8.42 (s, 1H), 7.94-7.91 (m, 2H), 7.82 (s, 1H), 7.29 (s, 1H), 5.06 (br s, 1H), 4.63 (dd, 2H), 4.03 (ddd AB, 2H), 3.95 (s, 3H), 3.91-3.86 (m, 3H), 3.31 (s, 3H); MS (EI) for $C_{22}H_{20}N_3O_5BrClF$: 542 (MH^+).

[0123] 1,4:3,6-Dianhydro-2-*O*-[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 11.20 (br s, 1H), 8.81 (s, 1H), 8.06 (s, 1H), 7.68-7.62 (m, 1H), 7.51 (d tr, 1H), 7.43 (s, 1H), 5.09 (br s, 1H), 4.66 (s, 2H), 4.07 (ddd AB 2H), 3.94 (s, 3H), 4.00-3.88 (m, 3H) 3.31 (s, 3H); MS (EI) for $C_{22}H_{20}N_3O_5ClF_2$: 480 (MH^+).

[0124] 1,4:3,6-Dianhydro-2-*O*-[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 9.69 (s,

1H), 8.42 (s, 1H), 7.94 (d, 1H), 7.84 (d, 1H), 7.82 (s, 1H), 7.29 (s, 1H), 4.63 (m, 2H), 4.03 (ddd AB, 2H), 3.95 (s, 3H), 3.91-3.86 (m, 3H), 3.31 (s, 3H); MS (EI) for $C_{22}H_{20}N_3O_5Cl_2F$: 496 (MH^+).

[0125] 1,4:3,6-Dianhydro-2-*O*-[4-[(3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 9.68 (s, 1H), 8.37 (s, 1H), 7.82 (s, 1H), 7.52-7.45 (m, 2H), 7.27 (d tr, 1H), 5.04 (br s, 1H), 4.63 (dd, 2H), 4.02 (ddd AB, 2H), 3.94 (s, 3H), 3.89 (br s, 1H), 3.87 (d 2H), 3.30 (s, 3H); MS (EI) for $C_{22}H_{21}N_3O_5ClF$: 462 (MH^+).

[0126] 1,4:3,6-Dianhydro-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 9.58 (s, 1H), 8.52 (s, 1H), 8.23 (d, 1H), 7.82-7.79 (m, 2H) 7.74 (d, 1H), 7.26 (s, 1H) 5.03 (br s , 1H), 4.62 (dd AB, 2H), 4.02 (ddd AB, 2H), 3.96 (s, 3H), 3.89 (br s, 1H), 3.85 (d, 2H) 3.30 (s, 3H); MS (EI) for $C_{22}H_{21}N_3O_5BrCl$: 524 (MH^+).

[0127] 1,4:3,6-Dianhydro-2-*O*-[4-[(3-bromo-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 9.65 (s, 1H), 8.30 (s, 1H), 7.86 (s, 1H), 7.57 (dd, 1H), 7.33 (d, 1H), 7.26-7.21 (m, 2H), 5.04 (br s, 1H), 4.63 (dd AB, 2H), 4.03 (ddd AB, 2H), 3.94 (s, 3H), 3.91 (br s, 1H), 3.87 (d, 2H), 3.31 (s, 3H); MS (EI) for $C_{23}H_{24}N_3O_5Br$: 502 (MH^+).

[0128] 1,4:3,6-Dianhydro-5-*O*-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl-D-glucitol: MS (EI) for $C_{22}H_{21}N_3O_5Cl_2$: 478 (MH^+).

[0129] 1,4:3,6-Dianhydro-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-difluoromethyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 9.64 (s, 1H), 8.56 (s, 1H), 8.26 (d, 1H), 7.86-7.82 (m, 2H), 7.77 (d, 1H), 7.31 (s, 1H), 6.84 (tr, 1H), 5.12 (br s, 1H), 4.74 (m, 2H), 4.06 (ddd AB, 2H), 3.98-3.90 (m, 6H); MS (EI) for $C_{22}H_{19}N_3O_5BrClF_2$: 558 ($MH^+$).

[0130] 1,4:3,6-Dianhydro-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-ethyl-L-iditol: ^1H NMR (400 MHz, d_6-DMSO): 9.62 (s, 1H), 8.55 (s, 1H), 8.26 (d, 1H), 7.85-7.82 (m, 2H), 7.76 (d, 1H), 5.04 (br s, 1H), 4.62 (dd AB, 2H), 4.15-4.09 (m, 1H), 4.00-3.95 (m, 5H), 3.95-3.82 (m, 2H), 3.57-3.48 (m, 2H), 1.13 (tr, 3H); MS (EI) for $C_{23}H_{23}N_3O_5BrCl$: 536 (MH^+).

[0131] 1,4:3,6-Dianhydro-5-deoxy-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-D-*xylo*-hexitol: ^{1}H NMR (400 MHz, d_6-DMSO): 9.62 (s, 1H), 8.55 (s, 1H), 8.26 (s, 1H), 7.85-7.82 (m, 2H), 7.76 (d, 1H), 7.30 (s, 1H), 4.98 (m, 1H), 4.80 (m, 1H), 4.51 (m, 1H), 4.18-4.14 (m, 1H), 3.97 (s, 3H), 3.92-3.81 (m, 3H), 2.01-1.97 (m, 2H); MS (EI) for $C_{21}H_{19}N_3O_4BrCl$: 492 (MH^+).

[0132] 1,4:3,6-Dianhydro-2-*O*-methyl-5-*O*-{6-(methyloxy)-4-[(2,3,4-trichlorophenyl)amino]quinazolin-7-yl}-L-iditol: ^{1}H NMR (400MHz; DMSO-d_6): 9.82 (br s, 1H), 8.36 (s, 1H), 8.86 (s, 1H), 7.75-7.73 (d, 1H), 7.60-7.58 (d, 1H), 7.29 (s, 1H), 5.06 (br s, 1H), 5.64-5.62 (m, 2H), 4.10-4.07 (dd, 1H), 4.02-4.01 (d, 1H), 3.97-3.94 (m, 1H), 3.95 (s, 3H), 3.93-3.90 (m, 1H), 3.88 (br m, 1H), 3.31 (s, 3H); MS (EI) for $C_{22}H_{20}Cl_3N_3O_5$: 511.91 (MH^+).

[0133] 1,4:3,6-Dianhydro-2-*O*-[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-iditol hydrochloride: ^{1}H NMR (400MHz; DMSO-d_6): 8.75 (s, 1H), 8.03 (s, 1H), 7.70-7.53 (m, 2H), 7.38 (s, 1H), 5.09-5.07 (m, 1H), 4.64-4.63 (br, 1H), 4.13-4.10 (dd, 1H), 4.02-4.01 (d, 1H), 3.99 (s, 3H), 3.93-3.92 (m, 1H), 3.89-3.88 (m, 2H), 3.31 (s, 3H); MS (EI) for $C_{22}H_{20}Cl_2FN_3O_5$: 495.96 (MH^+).

[0134] 1,4:3,6-Dianhydro-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-glucitol hydrochloride: ^{1}H NMR (400MHz; DMSO-d_6): 9.62 (br s, 1H), 8.53 (s, 1H), 8.24 (s, 1H), 7.93 (s, 1H), 7.81-7.81 (dd, 1H), 7.75-7.74 (d, 1H), 7.23 (s, 1H), 5.03-5.02 (d, 1H), 4.75-4.74 (tr, 1H), 4.59-4.58 (d, 1H), 4.12-4.10 (dd, 1H), 4.03-4.02 (d, 1H), 3.96 (s, 3H), 3.90-3.86 (m, 2H), 3.60-3.58 (dd, 1H), 2.88 (s, 3H); MS (EI) for $C_{22}H_{21}BrClN_3O_5$: 521.9 (MH^+).

Example 2

1,4:3,6-Dianhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-sorbose ethylene glycol acetal

[0135] 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal: A solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose (2.00g, 8.06 mmol), ethylene glycol (5.00g, 80.6 mmol), and *p*-toluenesulfonic acid (1.53g, 8.06 mmol) in benzene (100mL) was refluxed for 90 min using a Dean-Stark Trap apparatus. The reaction mixture was diluted with ethyl acetate (100mL), washed with saturated aqueous sodium bicarbonate

(2 x 50mL) then brine (50mL), and dried over anhydrous sodium sulfate. Filtration, concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 1.44g (61% yield) of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 8.08 (m, 2H), 7.58 (m, 1H), 7.54 (m, 2H), 5.38 (dd, 1H), 4.97 (t, 1H), 4.21-4.02 (m, 7H), 3.86 (d, 1H), 3.75 (d, 1H).

[0136] 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal: To a solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal (1.44g, 4.93 mmol) in methanol (40mL) was added 50% aqueous sodium hydroxide (0.38 g, 4.75 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 1M HCl, followed by concentration and column chromatography on silica (1:2 hexane/ethyl acetate) provided 0.74g (80% yield) of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 4.60 (t, 1H), 4.32 (m, 1H), 4.14 (d, 1H), 4.05-3.98 (m, 5H), 3.82 (s, 2H), 3.62 (dd, 1H), 2.65 (d, 1H).

[0137] 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal: To a solution of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal (0.74g, 3.93 mmol) and triethylamine (1.20g, 11.86 mmol) in dichloromethane (40mL) was added methanesulfonyl chloride (0.90g, 7.88 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 13 h. Dichloromethane (50mL) was added, and the organic layer was washed with saturated aqueous sodium bicarbonate (30mL), water (30mL), and brine (30mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 1.02g (97%) of 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$): 5.08 (m, 1H), 4.82 (t, 1H), 4.13 (dd, 1H), 4.04 (m, 4H), 3.93 (dd, 1H), 3.87 (d, 1H), 3.81 (d, 1H), 3.13 (s, 3H).

[0138] 1,4:3,6-dianhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)-quinazolin-7-yl]-L-sorbose ethylene glycol acetal: A suspension of 4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol (235mg, 0.48 mmol), 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal (190mg, 0.71 mmol), and potassium carbonate (329mg, 2.38 mmol) in DMF (10 mL) was stirred at 130°C under nitrogen for 14 h. The reaction mixture was poured into water (50mL), and extracted with ethyl acetate (3 x 30mL). The organic layers were washed with 5% LiCl (2 x 25mL), and brine (25mL) then dried over anhydrous sodium sulfate and concentrated. Filtration and column

chromatography on silica (9:1 dichloromethane/acetone to 7:3 dichloromethane/acetone) gave 77mg (29%) of 1,4:3,6-dianhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-sorbose ethylene glycol acetal as a off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.70 (s, 1H), 8.00 (d, 1H), 7.61 (d, 1H), 7.52 (dd, 1H), 7.31 (s, 1H), 7.14 (s, 1H), 7.00 (s, 1H), 4.98 (m, 1H), 4.86 (d, 1H), 4.42 (d, 1H), 4.32-4.23 (m, 2H), 4.10-4.05 (m, 4H), 4.00 (s, 3H), 3.86 (d, 1H), 3.78 (d, 1H); MS (EI) for $C_{23}H_{21}N_3O_6BrCl$: 550 (MH^+).

Example 3

1,4:3,6-Dianhydro-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-5-methylidene-D-xylo-hexitol:

[0139] 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(phenylcarbonyl)-D-*arabino*-hexitol (329mg, 1.34 mmol) in methanol (10mL) was added 50% aqueous sodium hydroxide (95mg, 1.19 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 4M hydrogen chloride in 1,4-dioxane followed by concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 141mg (74%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 5.37 (m, 1H), 5.20 (m, 1H), 4.80 (m, 1H), 4.54 (m, 2H), 4.43 (m, 1H), 4.26 (m, 1H), 3.95 (dd, 1H), 3.54 (dd, 1H), 2.70 (d, 1H).

[0140] 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol (135mg, 0.95 mmol) and triethylamine (288mg, 2.85 mmol) in dichloromethane (10mL) was added methanesulfonyl chloride (222mg, 1.94 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 18 h. Dichloromethane (50mL) was added and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 25mL), water (25mL) and brine (25mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 213mg (72%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$): 5.40 (m, 1H), 5.23 (m, 1H), 5.04 (m, 1H), 4.85 (m, 1H), 4.73 (t, 1H), 4.58 (m, 1H), 4.41 (m, 1H), 4.08 (dd, 1H), 3.86 (dd, 1H), 3.14 (s, 3H).

[0141] 1,4:3,6-dianhydro-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)-quinazolin-7-yl]-5-deoxy-5-methylidene-D-xylo-hexitol: A suspension of 4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol (425mg, 0.86 mmol), 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol (208mg, 0.94 mmol), and potassium carbonate (594mg, 4.30 mmol) in DMF (10 mL) was stirred at 130°C under nitrogen for 15 h. The reaction mixture was poured into water (50mL), and extracted with ethyl acetate (3 x 30mL). The organic layers were washed with 5% LiCl (2 x 25mL), and brine (25mL), dried over anhydrous sodium sulfate then filtered and concentrated. Column chromatography on silica (97:3 dichloromethane/ methanol) gave 234mg (54%) of 1,4:3,6-dianhydro-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-5-methylidene-D-xylo-hexitol as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.70 (s, 1H), 8.01 (d, 1H), 7.61 (d, 1H), 7.51 (dd, 1H), 7.36 (s, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 5.42 (m, 1H), 5.23 (m, 1H), 5.04 (d, 1H), 4.97 (t, 1H), 4.74 (d, 1H), 4.55 (m, 1H), 4.35 (m, 1H), 4.22 (m, 2H), 4.01 (s, 3H); MS (EI) for $C_{22}H_{19}N_3O_4BrCl$: 504 (MH^+).

Example 4

Methyl 3,6-anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl-α-D-idofuranoside

[0142] To a mixture of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-(D)-glycitol (4.32g, 17.3 mmol), triethylamine (4.91 mL, 35.3 mmol) and 4-dimethylaminopyridine (0.63g, 5.2 mmol) in dichloromethane (50 mL) at -10 ° to -15° was added trifluromethanesulfonic anhydride (3.48mL, 20.7 mmol) dropwise over ten minutes and the resulting mixture was stirred at this temperature for 3 hours. The mixture was poured into 100 mL of ice-water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered then concentrated. The crude triflate was suspended in toluene (50 mL) followed by addition of 1,8-diazabicyclo[4,5,0]undec-7-ene (5.25 mL, 34.6 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into ice-water and partitioned then the aqueous portion was extracted with dichloromethane (3 x 50 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate-hexane) to give 1,4:3,6-

dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol, as a white solid, 3.10g, 77% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.08-8.06 (m, 2H), 7.61-7.57 (m, 1H), 7.56-7.43 (m, 2H), 6.62-6.61 (d, 1H), 5.48-5.46 (m,1H), 5.32-5.26 (m,1H), 5.13-5.10 (m, 2H), 4.18-4.14 (tr,1H), 3.61-3.56 (tr, 1H).

[0143] Methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside: To a solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-arabino-hex-1-enitol (1.00g, 4.3 mmol) in methanol (17 mL) at -4°C was added 3-chloroperoxybenzoic acid (85%, 1.35g, 8.6 mmol), and the resulting mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction mixture was concentrated, diluted with dichloromthane (50 mL), washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 25-60% ethyl acetate-hexane) to give methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a white solid, 1.03g, 83% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.11-8.08 (d, 2H), 7.61-7.56 (tr, 1H), 7.48-7.44 (m, 2H), 5.24-5.17 (m, 2H), 4.96 (s, 1H), 4.57-4.56 (d, 1H), 4.27 (s, 1H), 4.22-4.18 (dd, 1H), 4.08-4.04 (dd, 1H) 3.36 (s, 3H).

[0144] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside: A mixture of methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (1.03g, 3.7 mmol), silver (I) oxide (0.85g, 3.7 mmol) and methyl iodide (0.34 mL, 5.5 mmol) in DMF (2 mL) was heated at 60°C for 1 hour. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (50 mL), filtered over celite, adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-30% ethyl acetate-hexane) to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a colorless oil, 0.82g, 76% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.11-8.09 (d, 2H), 7.60-7.56 (m, 1H), 7.46-7.44 (m, 2H), 5.24-5.20 (m, 1H), 5.18-5.09 (tr, 1H), 4.99 (s, 1H), 4.61-4.60 (d, 1H), 4.21-4.17 (tr, 1H), 4.08-4.03 (tr, 1H), 3.81 (s, 1H), 3.40 (s, 3H), 3.57 (s, 3H).

[0145] Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (820mg, 3.1mmol) and 50% sodium hydroxide (248 mg, 3.1 mmol) in methanol (10mL) was stirred at room temperature for 30 minutes. The material was adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to give methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside as a colorless oil, 420 mg, 85% yield. ^{1}H

NMR (400MHz; $CDCl_3$): 5.04 (s, 1H), 5.84-5.81 (tr, 1H), 4.44-4.42 (tr, 1H), 4.25-4.19 (m, 1H), 3.85-3.75 (m, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.75-2.72 (d, 1H).

[0146] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside: Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside (420 mg, 2.6 mmol) was dissolved in dichloromethane (10 mL) and pyridine (0.36 mL, 3.7 mmol) at 0°C. Methanesulfonyl chloride (0.14 mL, 3.1 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside as a colorless oil, 669mg, 95% yield, which was used without further purification.

[0147] Methyl 3,6-anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy) quinazolin-7-yl]-2-*O*-methyl-α-D-idofuranoside: Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside (314 mg, 1.1 mmol) was dissolved in DMF (3mL). To this solution was added potassium carbonate (404 mg, 2.9 mmol) and 4-[(4-bromo-3-chlorophenyl)amino]-6-methyloxy-7-hydroxyquinazoline trifluoroacetate (280 mg, 0.59 mmol). The resulting mixture was heated at 135°C for 18h. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (15 mL), washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 2-7% methanol in 1:1 ethyl acetate:hexanes) to give methyl 3,6-anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl-α-D-idofuranoside as a white solid, 181 mg, 28% yield. ^{1}H NMR (400MHz; Methanol-d_4): 8.75 (s, 1H), 8.04–8.06 (d, 1H), 7.99 (s, 1H), 7.78-7.75 (d, 1H), 7.64-7.61 (d, 1H), 7.35 (s, 1H), 5.16-5.14 (d, 1H), 5.02 (s, 1H), 4.89 (br, 1H), 4.69-4.68 (d, 1H) 4.46-4.42 (dd, 1H), 4.09 (br, 1H), 4.06 (s, 3H), 3.69(s, 1H), 3.48(s, 3H), 3.42 (s, 3H); MS (EI) for $C_{23}H_{23}BrClN_3O_6$: 551.88 (MH^+).

Example 5

Methyl 3,6-anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl-β-D-idofuranoside hydrochloride

[0148] 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose: A mixture of osmium tetroxide (4% in water, 0.25 mL, 0.03 mmol) and N-methylmorpholine (505 mg, 4.3 mmol)

in 3 mL of 50% acetone in water was warmed to 60°C. A solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol (2.00g, 8.6 mmol) in 6 mL of 50% acetone in water was added over 3 hours. During this time an additional amount of N-methylmorpholine (1.01g, 8.6 mmol) was added in small portions periodically. Upon completion of the addition process the reaction was stirred for another hour and cooled to room temperature. The crude mixture was applied to a column of silica gel and flashed (0-6% methanol in 1:1 ethyl acetate:hexane) to give 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as a white solid, 1.5g, 65% yield. ^{1}H NMR (400MHz; DMSO-d_6): 8.01-7.95, (m, 2H), 7.68-7.66 (m, 1H), 7.57-7.53 (m, 2H), 5.18-5.11 (m, 2H), 4.85-4.81 (m, 1H, m), 4.37-4.35 (m, 1H), 4.05-3.96 (m, 2H), 3.85-3.83 (m, 1H).

[0149] 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside: 3,6-Anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (576 mg, 2.2 mmol) was added to a mixture of sodium hydride (60% oil dispersion, 346 mg, 8.7 mmol) and methyl iodide (0.54mL, 8.7 mmol) in 5 mL of DMF at 0°C and the resulting mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate and quenched with water (5 mL). The aqueous portion was extracted with ethyl acetate (3 x 5 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate in hexane) to give 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside as a white solid, 270 mg, 42% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.09-8.07 (m, 2H), 7.61-7.57 (m, 1H), 7.48-7.27 (m, 2H), 5.25-5.22 (m, 1H), 5.07-5.06 (d, 1H), 4.94-4.91 (m, 1H), 4.73-4.71 (m, 1H), 4.20-4.16 (m, 1H), 3.96-3.94 (m, 1H), 3.85-3.83 (tr, 1H), 3.50 (s, 3H), 3.42 (s, 3H).

[0150] Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside (230mg, 0.92 mmol) and 50% sodium hydroxide (74 mg, 0.92 mmol) in methanol (5 mL) was stirred at room temperature for 30 minutes. The mixture was adsorbed on silica gel (2g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to afford a colorless oil which was employed directly in the next step, 140 mg, 0.72 mmol, 95% yield. The alcohol was dissolved in dichloromethane (5 mL) and pyridine (121 μL, 1.03 mmol) was added at 0°C. Methanesulfonyl chloride (27μL, 0.88 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours.

The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside as a colorless oil, 190 mg, 96% yield.

[0151] 3,6-Anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl-β-D-idofuranoside hydrochloride: Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside, (40 mg, 0.13 mmol) was dissolved in DMF (1mL). To this solution was added potassium carbonate (74 mg, 0.54 mmol) and 4-[(4-bromo-3-chlorophenyl)amino]-6-methyloxy-7-hydroxyquinazolin trifluoroacetate (64 mg, 0.13 mmol). The resulting mixture was heated at 135°C for 18h. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (5 mL), washed with water, dried over anhydrous sodium sulfate, filtered, concentrated. The residue was purified by flash chromatography (silica gel, 2-7% methanol in 1:1 ethyl acetate:hexanes) to give a white solid which was further purified by preparative reverse phase HPLC and the pure fractions lyophilized to give a white solid. The solid was dissolved in methanol (2 mL) and 4N hydrogen chloride in dioxane (2mL) was added and the mixture evaporated *in vacuo*. This evaporation process was repeated three times to give methyl 3,6-anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl-β-D-idofuranoside hydrochloride, 9.2 mg, 12% yield, as a white solid. ^{1}H NMR (400MHz; Methanol-d_4): 8.75 (s, 1H), 8.07-8.06 (d, 1H), 8.00 (s, 1H), 7.79-7.77 (d, 1H), 7.64-7.62 (dd, 1H), 7.29 (s, 1H), 5.16-5.15 (d, 1H), 5.09-5.08 (d, 1H), 4.79-4.71 (m, 2H), 4.24-4.18 (m, 2H), 4.07 (s, 3H), 3.89-3.87 (tr, 1H), 3.45 (s, 3H), 3.43 (s, 3H); MS (EI) for $C_{23}H_{23}BrClN_3O_6$: 551.82 (MH^+).

Example 6

3,6-Anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-1,2-*O*-(1-methylethylidene)-β-D-idofuranose

[0152] 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose A mixture of 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (1.00g), 2,2-dimethoxy propane (0.63 mL), p-toluenesulfonic acid (20 mg) and benzene (10 mL) was heated at reflux for 3 hours. The reaction mixture was cooled then adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-35% ethyl acetate in hexanes) to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as colorless oil, 0.85g,

74% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.08-8.06 (d, 2H), 7.59-7.56 (tr, 1H), 7.46-7.42 (m, 2H), 5.99-5.98 (d, 1H), 5.35-5.31 (tr, 1H), 5.10-5.08 (d, 1H), 4.66-4.65 (d, 1H), 4.61-4.60 (d, 1H), 4.20-4.16 (dd, 1H), 3.91-3.74 (tr, 1H,), 1.50 (s, 3H), 1.34 (s, 3H).

[0153] 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose: A solution of 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (850mg) and 50% sodium hydroxide (111 mg) in methanol (10mL) was stirred at room temperature for 30 minutes. The mixture was then adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) and the alcohol intermediate, 390 mg, 70% yield, was used immediately in the next step. The alcohol was dissolved in dichloromethane (10 mL) and pyridine (0.32 mL) at 0°C. Methanesulfonyl chloride (0.12 mL) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose as a colorless oil, 485 mg, 90% yield, which was immediately employed in the next step.

[0154] 3,6-Anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-1,2-*O*-(1-methylethylidene)-β-D-idofuranose: 3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose, (85 mg, 0.30 mmol) was dissolved in DMF (3mL). To this solution was added potassium carbonate (168 mg, 1.21 mmol) and 4-[(4-bromo-3-chlorophenyl)amino]-6-methyloxy-7-hydroxyquinazoline trifluoroacetate (145 mg, 0.30 mmol). The resulting mixture was heated at 135°C for 18h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (15 mL), washed with water, dried over anhydrous sodium sulfate, filtered, concentrated. The residue was purified by flash chromatography (silica gel, 2-7% Methanol in 1:1 ethyl acetate:hexanes) to give 3,6-anhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-1,2-*O*-(1-methylethylidene)-β-D-idofuranose, 121 mg, 77% yield, as a white solid. ^{1}H NMR (400MHz; Methanol-d_4): 8.48 (s, 1H), 8.17-8.16 (d, 1H), 7.76 (s, 1H), 7.70-7.61 (m, 2H), 7.19 (s, 1H), 5.95-5.94 (d, 1H), 5.18-5.17 (d, 1H), 4.93-4.91 (m, 1H), 4.70-4.62 (m, 2H), 4.28-4.22 (dd, 1H), 4.08-4.06 (d, 1H), 4.03 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H); MS (EI) for $C_{24}H_{23}BrClN_3O_6$: 563.83 (MH^+).

Example 7

(3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine and (3*R*,8a*S*)-3-(chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine

[0155] (*S*)-(+)-Prolinol (6.00 g, 59.3 mmol) was added to epichlorohydrin (47 mL, 600 mmol) at 0°C. The solution was stirred at 40°C for 0.5 h and then concentrated *in vacuo*. The residual oil was cooled in an ice bath and concentrated sulfuric acid (18 mL) was added dropwise with stirring. The mixture was heated at 170-180°C for 1.5 h, poured into ice (300 mL) and then basified with sodium carbonate to pH~8. The mixture was partitioned with ethyl acetate/hexanes and filtered. The filtrate was separated and the aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an oil which was purified by column chromatography (ethyl acetate for less polar product and then 30% methanol in ethyl acetate). (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (less polar product) (1.87 g, 10.7 mmol, 18% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 4.06 (dd, 1H), 3.79-3.71 (m, 1H), 3.60-3.48 (m, 2H), 3.36 (dd, 1H), 3.15 (dd, 1H), 3.13-3.06 (m, 1H), 2.21-2.01 (m, 3H), 1.90-1.68 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+). (3*R*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (1.54 g, 8.77 mmol, 15% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.94-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.29-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.38 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

[0156] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following reagents were prepared:

[0157] (3*R*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.79-3.70 (m, 1H), 3.61-3.48 (m, 2H), 3.35 (dd, 1H), 3.15 (dd, 1H), 3.13-3.07 (m, 1H), 2.21-2.01 (m, 3H), 1.89-1.67 (m, 3H), 1.39-1.25 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

[0158] (3*S*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine: ^{1}H NMR (400 MHz, $CDCl_3$): 3.93-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.30-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.37 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

Example 8

N-(4-Bromo-2,3-dichlorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride

[0159] *N*-(4-bromo-2,3-dichlorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (115 mg, 0.655 mmol) and 4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetic acid salt (347 mg, 0.655 mmol) were dissolved in dimethylacetamide (0.8 mL) and potassium carbonate (452 mg, 3.28 mmol) was added. The mixture was stirred at 130°C for 36 h. The mixture was cooled to room temperature and the mixture was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate and the combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (ethyl acetate-ethanol 1:1). The purified material was dissolved in ethanol and treated with 4M solution of HCl in 1,4-dioxane (0.25 mL) and the mixture was concentrated *in vacuo*. The residue was dissolved in water and lyophilized to afford *N*-(4-bromo-2,3-dichlorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride as a brown solid (131 mg, 0.222 mmol, 34% yield). ^{1}H NMR (400 MHz, d_6-DMSO): 11.9-11.5 (m, 2H), 8.79 (s, 1H), 8.34 (s, 1H), 7.96 (d, 1H), 7.54 (d, 1H), 7.41 (s, 1H), 4.47-4.25 (m, 4H), 4.03 (s, 3H) 3.96-3.00 (m, 6H), 2.18-1.88 (m, 3H), 1.73-1.57 (m, 1H); MS (EI) for $C_{23}H_{23}N_4O_3Cl_2Br$: 553 (MH^+).

[0160] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0161] *N*-(3,4-Dichlorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 11.5-11.2 (m, 2H), 8.86 (s, 1H), 8.32 (s, 1H), 8.13 (s, 1H), 7.79 (dd, 1H), 7.73 (d, 1H), 7.37 (s, 1H), 4.45-4.24 (m, 4H), 4.03 (s, 3H) 3.93-3.00 (m, 6H), 2.20-1.90 (m, 3H), 1.74-1.56 (m, 1H); MS (EI) for $C_{23}H_{24}N_4O_3Cl_2$: 475 (MH^+).

[0162] *N*-(3,4-Dichlorophenyl)-7-{[(3*R*,8a*R*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 11.6-11.3 (m, 2H), 8.86 (s, 1H), 8.32 (s, 1H), 8.14 (s, 1H), 7.80 (dd, 1H), 7.73 (d,

1H), 7.35 (s, 1H), 4.45-4.25 (m, 4H), 4.03 (s, 3H) 3.96-2.98 (m, 6H), 2.19-1.89 (m, 3H), 1.72-1.57 (m, 1H); MS (EI) for $C_{23}H_{24}N_4O_3Cl_2$: 475 (MH^+).

[0163] *N*-(3,4-Dichlorophenyl)-7-{[(3*R*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 11.6-11.4 (m, 2H), 8.89 (s, 1H), 8.42 (s, 1H), 8.18 (d, 1H), 7.84 (dd, 1H), 7.75 (d, 1H), 7.40 (s, 1H), 4.32 (d, 2H), 4.23-4.15 (m, 1H), 4.09-3.95 (m, 2H), 4.05 (s, 3H), 3.70-3.03 (m, 5H), 2.14-2.04 (m, 4H); MS (EI) for $C_{23}H_{24}N_4O_3Cl_2$: 475 (MH^+).

[0164] *N*-(3,4-Dichlorophenyl)-7-{[(3*S*,8a*R*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 11.7-11.5 (m, 2H), 8.90 (s, 1H), 8.49 (s, 1H), 8.18 (d, 1H), 7.86 (dd, 1H), 7.75 (d, 1H), 7.42 (s, 1H), 4.31 (d, 2H), 4.24-4.16 (m, 1H), 4.09-3.95 (m, 2H), 4.06 (s, 3H), 3.69-3.04 (m, 5H), 2.14-2.03 (m, 4H); MS (EI) for $C_{23}H_{24}N_4O_3Cl_2$: 475 (MH^+).

Example 9

N-(3,4-Dichloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride

[0165] (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate: (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (2.30 g, 13.1 mmol) and potassium acetate (12.8 g, 131 mmol) were stirred in dimethylformamide (25 mL) at 140°C for 20 h. The mixture was partitioned between ethyl acetate and water. The organic portion was washed twice with water, then with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate as a brown oil (2.53 g, 12.7 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.14-4.02 (m, 3H), 3.81-3.72 (m, 1H), 3.37-3.31 (m, 1H), 3.09 (dt, 1H), 3.00 (dd, 1H), 2.21-2.00 (m, 3H), 2.10 (s, 3H), 1.90-1.67 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_{10}H_{17}NO_3$: 200 (MH^+).

[0166] (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate (2.36 g, 11.9 mmol) was treated with sodium methoxide (25 wt% solution in methanol; 2.7 mL) for 0.5 h. The mixture was cooled in an ice bath and a solution of 4M HCl in 1,4-dioxane (3 mL, 12.0 mmol) was added slowly. The mixture was stirred at room temperature for 5 minutes and then was

concentrated *in vacuo* to afford a suspension which was diluted with dichloromethane, filtered and the filtrate was concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol as a brown oil (1.93 g, >100% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.73-3.65 (m, 2H), 3.62-3.56 (m, 1H), 3.39-3.34 (m, 1H), 3.10 (dt, 1H), 3.00-2.95 (m, 1H), 2.24-1.98 (m, 4H), 1.97-1.70 (m, 3H), 1.44-1.28 (m, 1H); MS (EI) for $C_8H_{15}NO_2$: 158 (MH^+).

[0167] (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl methanesulfonate: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol (1.00 g, 6.37 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (2.4 mL, 17.3 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.93 mL, 12.0 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic portion was washed with saturated sodium bicarbonate solution. The combined aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl methanesulfonate as an orange-brown oil (1.20 g, 5.1 mmol, 80% yield). MS (EI) for $C_9H_{17}NO_4S$: 236 (MH^+).

[0168] *N*-(3,4-dichloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: 4-[(3,4-Dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetic acid salt (307 mg, 0.655 mmol) was dissolved in dimethylformamide (1 mL) and potassium carbonate (452 mg, 3.28 mmol) was added followed by (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl methanesulfonate (250 mg, 1.06 mmol). The mixture was stirred at 70°C for 41 h and then was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil which was purified by column chromatography (ethyl acetate-ethanol 1:1). The purified material was dissolved in methanol and treated with 4M solution of HCl in 1,4-dioxane (0.1 mL) and the mixture was concentrated *in vacuo* to afford *N*-(3,4-dichloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride as a pale yellow solid (66 mg, 0.125 mmol, 19% yield). ^{1}H NMR (400 MHz, d_6-DMSO):

11.9-11.5 (m, 2H), 8.83 (s, 1H), 8.39-8.35 (m, 1H), 7.69 (dd, 1H), 7.62 (dd, 1H), 7.43 (s, 1H), 4.48-4.24 (m, 4H), 4.04 (s, 3H), 3.97-3.85 (m, 1H), 3.78-2.96 (m, 5H), 2.17-1.90 (m, 3H), 1.72-1.58 (m, 1H); MS (EI) for $C_{23}H_{23}N_4O_3FCl_2$: 493 (MH^+).

[0169] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0170] *N*-(3-Chloro-2,4-difluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 11.9-11.6 (m, 2H), 8.84 (s, 1H), 8.41-8.37 (m, 1H), 7.67-7.60 (m, 1H), 7.51 (dt, 1H), 7.41 (s, 1H), 4.48-4.24 (m, 4H), 4.04 (s, 3H), 3.97-3.86 (m, 1H), 3.80-2.96 (m, 5H), 2.18-1.90 (m, 3H), 1.72-1.59 (m, 1H); MS (EI) for $C_{23}H_{23}N_4O_3F_2Cl$: 477 (MH^+).

[0171] *N*-(4-Bromo-3-chloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.70 (s, 1H), 8.49 (dd, 1H), 7.49 (dd, 1H), 7.29 (s, 1H), 6.98 (s, 1H), 4.25 (dd, 1H), 4.17 (dd, 1H), 4.13-4.06 (m, 2H), 4.03 (s, 3H), 3.46-3.38 (m, 1H), 3.20 (dd, 1H), 3.14 (dt, 1H), 2.28-2.17 (m, 2H), 2.17-2.07 (m, 1H), 1.90-1.71 (m, 3H), 1.42-1.30 (m, 1H); MS (EI) for $C_{23}H_{23}N_4O_3FClBr$: 537 (MH^+).

[0172] *N*-(4,5-Dichloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.91 (d, 1H), 8.71 (s, 1H), 7.29-7.26 (m, 2H), 6.94 (s, 1H), 4.24 (dd, 1H), 4.16 (dd, 1H), 4.11-4.04 (m, 2H), 4.02 (s, 3H), 3.44-3.38 (m, 1H), 3.19 (dd, 1H), 3.13 (dt, 1H), 2.28-2.17 (m, 2H), 2.16-2.07 (m, 1H), 1.91-1.69 (m, 3H), 1.42-1.30 (m, 1H); MS (EI) for $C_{23}H_{23}N_4O_3FCl_2$: 493 (MH^+).

[0173] *N*-(4-Bromo-5-chloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.95 (d, 1H), 8.72 (s, 1H), 7.43 (d, 1H), 7.28 (s, 1H), 6.93 (s, 1H), 4.24 (dd, 1H), 4.15 (dd, 1H), 4.12-4.04 (m, 2H), 4.02 (s, 3H), 3.44-3.37 (m, 1H), 3.19 (dd, 1H), 3.13 (dt, 1H), 2.27-2.16 (m, 2H), 2.16-2.06 (m, 1H), 1.90-1.69 (m, 3H), 1.42-1.28 (m, 1H); MS (EI) for $C_{23}H_{23}N_4O_3FClBr$: 537 (MH^+).

Example 10

N-(3,4-Dichloro-2-fluorophenyl)-6-(methyloxy)-7-[(octahydro-2*H*-quinolizin-3-ylmethyl)oxy]quinazolin-4-amine

[0174] Octahydro-2*H*-quinolizin-3-ylmethanol: Ethyl octahydro-2*H*-quinolizine-3-carboxylate (2.35 g, 11.1 mmol) was added dropwise to a stirred suspension of lithium aluminum hydride (1 M solution in tetrahydrofuran, 33 mL, 33 mmol) in tetrahydrofuran (50 mL) at 0°C. The reaction was stirred at room temperature for 3 h. The mixture was cooled in an ice bath and ethyl acetate (6 mL) was added slowly, followed by water (1.25 mL), 15% aqueous sodium hydroxide solution (5 mL) and water (1.25 mL). The mixture was filtered through a pad of celite and washed with ether. The filtrate was concentrated *in vacuo* and dried rigorously to afford octahydro-2*H*-quinolizin-3-ylmethanol as a yellow oil (1.66 g, 9.82 mmol, 88% yield). MS (EI) for $C_{10}H_{19}NO$: 170 (MH^+).

[0175] Octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate: Octahydro-2*H*-quinolizin-3-ylmethanol (600 mg, 3.55 mmol) was dissolved in dichloromethane (8 mL) and triethylamine (1.5 mL, 10.8 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.56 mL, 7.16 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate as an orange oil (796 mg, 3.22 mmol, 91% yield). MS (EI) for $C_{11}H_{21}NO_3S$: 248 (MH^+).

[0176] *N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-[(octahydro-2*H*-quinolizin-3-ylmethyl)oxy]quinazolin-4-amine: 4-[(3,4-Dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-ol hydrochloride (469 mg, 1.20 mmol) was dissolved in dimethylformamide (1 mL) and potassium carbonate (828 mg, 6.00 mmol) was added followed by octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate (466 mg, 1.89 mmol) in dimethylformamide (1 mL). The mixture was stirred at 70°C for 38 h and then was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (15-20% methanol in dichloromethane). The purified material was crystallized from

methanol to afford *N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-[(octahydro-2*H*-quinolizin-3-ylmethyl)oxy]quinazolin-4-amine as a cream colored solid (83.4 mg, 0.165 mmol, 14% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.69 (s, 1H), 8.53 (t, 1H), 7.34 (dd, 1H), 7.28-7.22 (m, 1H), 7.23 (s, 1H), 6.98 (s, 1H), 4.06-3.95 (m, 2H), 4.02 (s, 3H), 3.09 (d, 1H), 2.87 (d, 1H), 2.43-2.27 (m, 1H), 2.10-1.97 (m, 1H), 1.95-1.84 (m, 2H), 1.80-1.52 (m, 5H), 1.46-0.95 (m, 5H); MS (EI) for $C_{25}H_{27}N_4O_2FCl_2$: 505 (MH^+).

Example 11

(3*S*,8a*S*)-3-({[4-[(3,4-Dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[0177] (3*S*,8a*S*)-3-(Hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: A solution of methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (3.50 g, 10.4 mmol) in methanol was added to 5% palladium on carbon (50 wt.% in water) in methanol and treated with hydrogen at 40 psi for 1 h. The mixture was filtered and the filtrate was brought to reflux briefly and then cooled and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a colorless solid (1.50 g, 8.83 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.22 (m, 1H), 3.83-3.75 (m, 1H), 3.69 (dd, 1H), 3.56 (dd, 1H), 3.31 (t, 1H), 3.08 (dd, 1H), 2.92 (dt, 1H), 2.76-2.70 (m, 1H), 2.66 (dd, 1H), 2.28-2.16 (m, 1H), 2.02-1.73 (m, 3H); MS (EI) for $C_8H_{14}N_2O_2$: 171 (MH^+).

[0178] (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: To a solution of (3*S*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.49 g, 8.82 mmol) in dimethylformamide (20 mL) was added triethylamine (2.45 mL, 17.6 mmol) and 4-dimethylaminopyridine (90 mg, 0.882 mmol). The solution was cooled in an ice bath and *tert*-butyldimethylsilyl chloride (2.66 g, 17.6 mmol) was added. The mixture was warmed to room temperature and stirred for 14 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a pale brown solid which was triturated with ethyl acetate to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as an

off-white solid (1.74 g, 5.84 mmol, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 6.09-5.90 (m, 1H), 3.86-3.76 (m, 1H), 3.63 (dd, 1H), 3.44 (dd, 1H), 3.25 (t, 1H), 3.10 (ddd, 1H), 2.98-2.90 (m, 1H), 2.68-2.60 (m, 1H), 2.52 (dd, 1H), 2.28-2.18 (m, 1H), 2.06-1.95 (m, 1H), 1.93-1.74 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); MS (EI) for $C_{14}H_{28}N_2O_2Si$: 285 (MH^+).

[0179] (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydro pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.51g, 5.32mmol) in dimethylformamide (8 mL) was added to an ice-cooled suspension of sodium hydride (60 wt.% dispersion in oil; 213 mg, 5.32 mmol) in dimethylformamide (8 mL). The mixture was stirred at 0°C for 0.25 h and then iodomethane (0.332 mL, 5.32 mmol) was added dropwise. The mixture was stirred at room temperature for 0.5 h and then was stirred at 70°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (1.552 g, 5.21 mmol) which was dissolved in tetrahydrofuran (20 mL) and treated with tetrabutylammonium fluoride (1.0M solution in tetrahydrofuran; 10.4 mL, 10.4 mmol) for 2 h at room temperature. The mixture was concentrated *in vacuo* and purified by column chromatography (10% methanol in dichloromethane) to afford (3*S*,8a*S*)-3-(hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (496mg, 2.70mmol, 51% yield from (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one). ^{1}H NMR (400 MHz, $CDCl_3$): 3.98-3.93 (m, 1H), 3.86 (dd, 1H), 3.61-3.55 (m, 1H), 3.29-3.25 (m, 1H), 3.09-3.03 (m, 1H), 3.03-2.97 (m, 1H), 3.02 (s, 3H), 2.93 (dd, 1H), 2.87-2.79 (m, 1H), 2.32-2.21 (m, 1H), 2.00-1.86 (m, 2H), 1.83-1.64 (m, 1H); MS (EI) for $C_9H_{16}N_2O_2$: 185 (MH^+).

[0180] (3*S*,8a*S*)-3-({[4-[(3,4-Dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: (3*S*,8a*S*)-3-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (505 mg, 2.74 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.8 mL, 5.75 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.45 mL, 5.81 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was

concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford [(3*S*,8a*S*)-2-methyl-1-oxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]methyl methanesulfonate as an orange oil (538 mg, 2.05 mmol, 75% yield). 4-[(3,4-Dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-ol hydrochloride (469 mg, 1.20 mmol) was dissolved in dimethylformamide (1 mL) and potassium carbonate (828 mg, 6.00 mmol) was added followed by [(3*S*,8a*S*)-2-methyl-1-oxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl]methyl methanesulfonate (538 mg, 2.05 mmol) in dimethylformamide (1 mL). The mixture was stirred at 70°C for 34 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography (6-8% methanol in dichloromethane) to afford a yellow foam (300 mg, 0.577 mmol, 48% yield). The yellow foam (100 mg) was purified further by column chromatography (ethyl acetate-ethanol 1:1) to afford (3*S*,8a*S*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow solid (60 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 8.71 (s, 1H), 8.52 (dd, 1H), 7.36-7.32 (m, 2H), 7.01 (s, 1H), 4.49 (dd, 1H), 4.34 (dd, 1H), 4.03 (s, 3H), 3.90-3.84 (m, 1H), 3.47 (t, 1H), 3.13 (s, 3H), 3.05 (dd, 1H), 2.95 (dd, 1H), 2.93-2.83 (m, 2H), 2.29-2.19 (m, 1H), 2.03-1.84 (m, 2H), 1.83-1.70 (m, 1H); MS (EI) for $C_{24}H_{24}N_5O_3FCl_2$: 520 (MH^+).

Example 12

(3*S*,8a*S*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[0181] 1,2-Dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol: To a solution of 2-deoxy-2-{[(phenylmethyloxy) carbonyl]amino}-D-glycero-hexopyranose (5.0 g, 0.016 mol) in methanol (500 mL) was added L-proline methyl ester hydrochloride (2.8 g, 0.022 mol) and sodium cyanoborohydride (3.4 g, 0.054 mol). The solution was heated to 64 °C for 14 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to afford 1,2-dideoxy-1-[(2*S*)-2-

(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy)carbonyl]amino]-D-*glycero*-hexitol (6.81 g, 100%) as a clear and colorless oil. MS (EI) for $C_{20}H_{31}N_2O_8$: 427 (MH^+).

[0182] Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate: 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol (6.81 g, 0.016 mol) was taken into water (100 mL) and the resulting solution was cooled to 0°C. Sodium periodiate (14.8 g, 0.069 mol) dissolved in water was added dropwise and the resulting mixture was stirred at 0°C for 2 h. The reaction mixture was partitioned with dichloromethane (3x100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was taken up in methanol (200 mL) and the resulting solution was cooled to 0°C. Sodium borohydride (1.98 g, 0.052 mol) was added and the reaction mixture was stirred for 1 h at 0°C. The reaction mixture was concentrated *in vacuo* and partitioned with dichloromethane and saturated aqueous ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (5% methanol in dichloromethane) to yield methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (4.9 g, 92%) as a white solid. MS (EI) for $C_{17}H_{25}N_2O_5$: 337 (MH^+).

[0183] Methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate: Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate (200 mg, 0.594 mmol) was dissolved in dichloromethane (5 mL) followed by the addition of 4-(dimethylamino)pyridine (3.6 mg, 0.039 mmol) and triethylamine (0.125 mL, 0.891 mmol) and the resulting mixture was cooled to 0 °C. Methanesulfonyl chloride (0.060 mL, 0.773 mmol) was added dropwise and the reaction mixture was stirred for 1 h at 0°C. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (246 mg, 100%) as a clear and colorless oil. MS (EI) for $C_{18}H_{27}N_2O_7S$: 415 (MH^+).

[0184] methyl (1*R*)-2-[(2*S*)-3-{[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy) quinazolin-7-yl]oxy}-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]cyclopentane carboxylate: 4-[(3,4-dichloro-2-fluorophenyl)amino-6-(methyloxy)quinazolin-7-ol

hydrochloride (400 mg, 1.02 mmol) and methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (603 mg, 1.45 mmol) were suspended in DMF (5 mL) and powdered potassium carbonate (705 mg, 5.10 mmol) was added. The mixture was stirred at 70°C for 12 h. The reaction mixture was filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% methanol in dichloromethane) to yield methyl (1*R*)-2-[(2*S*)-3-{[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}-2-({[(phenylmethyl)oxy] carbonyl}amino)propyl]cyclopentanecarboxylate (686 mg, 100%) as a yellow oil. MS (EI) for $C_{32}H_{32}Cl_2FN_5O_6$: 672 (M^+).

[0185] (3*S*,8a*S*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: Methyl (1*R*)-2-[(2*S*)-3-{[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}-2-({[(phenylmethyl) oxy]carbonyl}amino)propyl]cyclopentanecarboxylate (686mg, 1.02 mmol) was diluted with glacial acetic acid (3 mL) and 30wt% hydrogen bromide in acetic acid (2 mL) was added. The resulting mixture was stirred for 13 h and then concentrated *in vacuo*. The crude residue was taken up in methanol (5 mL) followed the addition of powdered potassium carbonate (700 mg, 5.07 mmol) at room temperature. The resulting mixture was stirred for 7 h, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% methanol in dichloromethane) to yield the title compound (181 mg, 35%) as a yellow solid. ^{1}H NMR (400 MHz, d_4-MeOH): 8.34 (s, 1H), 7.75 (s, 1H), 7.76-7.55 (m, 1H), 7.45-7.40 (dd, 1H), 7.17 (s, 1H), 4.30-4.25 (m, 1H), 4.20-4.15 (m, 2H), 4.03 (s, 3H), 3.78-3.70 (m, 1H), 3.65-3.60 (m, 1H), 3.55-3.50 (m, 1H), 3.32-3.29 (m, 2H), 3.00-2.95 (m, 2H), 2.83-2.78 (m, 2H), 2.25-2.15 (m, 2H); MS (EI) for $C_{23}H_{23}Cl_2FN_5O_3$: 507 (MH^+).

[0186] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0187] (3*S*,8a*R*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one: $C_{23}H_{23}Cl_2FN_5O_3$: 507 (MH^+).

[0188] (3*S*, 8a*S*)-3-({[4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}-methyl)hexahydropyrrolo[1,2-a]pyrazin-1-(2H)-one: ^{1}H NMR (400 MHz, d_4-MeOH): 8.36 (s, 1H), 7.71 (s, 1H). 7.60-7.55 (m, 2H), 7.18 (s, 1H), 4.29-4.22 (m, 1H), 4.19-4.14 (m, 1H), 4.02 (s, 3H), 3.99-3.92 (m, 1H), 3.36-3.30 (m, 1H), 3.32-3.90 (m, 2H), 2.82-

2.74 (m, 1H), 2.26-2.10 (m, 1H), 2.19-2.18 (m, 3H), 1.30-1.20 (m, 2H), 0.90-0.80 (m, 1H); MS (EI) for $C_{23}H_{23}BrClN_5O_3$: 551 (MH^+).

[0189] (3*S*, 9a*S*)-3-({[4-[(3, 4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one: $C_{24}H_{25}Cl_2FN_5O_3$: 521 (MH^+).

[0190] (3*S*, 9a*R*)-3-({[4-[(3, 4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one: $C_{24}H_{25}Cl_2FN_5O_3$: 521 (MH^+).

Example 13

N-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta [*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride

[0191] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: Under a nitrogen atmosphere, borane tetrahydrofuran complex (1M in THF, 42 mL, 41.9 mmol) was diluted with tetrahydrofuran (42 mL) and cooled with an ice bath. Neat 2,3-dimethylbut-2-ene (5.0 mL, 41.9 mmol) was added in portions over 0.25 h and the solution was stirred at 0°C for 3 h. A solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-methylidenehexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (1.98 g, 8.88 mmol) in tetrahydrofuran (10 mL) was added slowly, and the solution was warmed to room temperature and stirred 12 h. After cooling to 0°C, 10% aqueous sodium hydroxide (17 mL, 41.7 mmol) was added slowly, followed by 30% aqueous hydrogen peroxide (13 mL, 128 mmol) and the solution was warmed to room temperature. The solvent was removed *in vacuo* and the solution was partitioned between water and diethyl ether. The layers were separated and the aqueous layer was further extracted (3 x 50 mL diethyl ether). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 2.04 (95%) of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate, which was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (broad s, 1H), 3.66-3.46 (m, 3H), 3.20-3.00 (m, 2H), 2.70-2.59 (m, 2H), 2.37-2.18 (m, 1H), 2.04 (m, 1H), 1.84 (broad s, 1H), 1.70-1.55 (m, 1H), 1.46 (s, 9H), 1.17 (m, 1H), 0.93 (m, 1H).

[0192] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta [*c*]pyrrole-2(1*H*)-carboxylate Methanesulfonyl chloride (0.2mL, 2.48mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydro

cyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.40 g, 1.65 mmol) and triethylamine (0.69 mL, 4.95 mmol) in 20 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous sodium hydroxide, brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{14}H_{25}NO_5S$: 320 (MH^+), 264 (M-tBu).

[0193] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: A solution of 4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetate (salt) (0.217g, 0.425mmol), 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (0.163g, 0.510 mmol), potassium carbonate (0.290 g, 2.12 mmol) in N,N-dimethylacetamide (1.6 mL) was heated in a sealed reaction tube at 90°C for 12 h. The crude reaction mixture was diluted with 100 mL of 10% methanol in ethyl acetate and washed with water (5 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 3:1 hexanes:acetone) provided 1,1-dimethylethyl (3a*R*,6a*S*)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate which was used directly in the next step. MS (EI) for $C_{28}H_{31}N_4O_4FClBr$: 623 (MH^+).

[0194] *N*-(4-Bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine hydrochloride: 1,1-Dimethylethyl (3a*R*,6a*S*)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate derivative was taken up in methanol (50 mL) and treated with 4.0M hydrogen chloride in dioxane (excess) and heated briefly to reflux. Concentration *in vacuo* gave *N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine hydrochloride which was used directly in the next step. ^1H NMR (400 MHz, d_4-MeOH): 8.70 (s, 1H), 7.97 (s, 1H), 7.68 (d, 1H), 7.49 (t, 1H), 7.28 (s, 1H), 4.25 (m, 2H), 4.08

(s, 3H), 3.57 (m, 1H), 3.02 (m, 4H), 2.80-2.60 (m, 2H), 2.35 (m, 1H), 1.89 (m, 4H), 1.40 (m, 1). MS (EI) for $C_{23}H_{23}N_4O_2FClBr$: 522 (MH^+).

[0195] *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: N-(4-Bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta-[*c*]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine hydrochloride was solubilized in formic acid (3.0 mL) and 37% aqueous formaldehyde (0.5 mL, 2.55 mmol) was added. The solution was heated to 95°C for 12 h and additional formaldehyde (1.0 mL, 5.10 mmol) was added. After heating an additional 12 h, the reaction mixture was concentrated *in vacuo*. The residue was taken up in methanol and treated with Bio-Rad AG 1-X8 resin hydroxide form until pH 8. The product was filtered, concentrated *in vacuo*, and purified by HPLC (reverse-phase, water/acetonitrile/0.1% TFA). Upon removal of solvent, the product was taken up in methanol and treated with Bio-Rad AG 1-X8 resin hydroxide form until pH 8. The product was filtered and concentrated *in vacuo* then taken up in fresh methanol and treated with 4.0 M hydrogen chloride in dioxane (0.05 mL). Removal of solvent *in vacuo* provided 54.1 mg (24%) of *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride. ^1H NMR (400 MHz, d_6-DMSO): 8.83 (d, 1H), 8.33 (s, 1H), 7.80 (d, 1H), 7.56 (t, 1H), 7.40 (s, 1H), 4.16 (m, 2), 4.01 (s, 3H), 3.80-3.68 (m, 1H), 3.05 (m, 2H), 2.90-2.70 (m, 5H), 2.34 (m, 1H), 2.15 (m, 2H), 1.75 (m, 1H), 1.57 (m, 2H), 1.35 (m, 1H). MS (EI) for $C_{24}H_{25}N_4O_2FClBr$: 537 (MH^+).

[0196] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0197] *N*-(4-bromo-5-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: ^1H NMR (400 MHz, d_6-DMSO): 8.83 (d, 1H), 8.33 (s, 1H), 8.03 (d, 1H), 7.93 (d, 1H), 7.41 (m, 1H), 4.16 (m, 2), 4.02 (s, 3H), 3.70 (m, 1H), 3.05 (m, 2H), 2.91-2.75 (m, 5H), 2.34 (m, 1H), 2.16 (m, 2H), 1.75 (m, 1H), 1.57 (m, 2H), 1.35 (m, 1H). MS (EI) for $C_{24}H_{25}N_4O_2FClBr$: 537 (MH^+).

[0198] *N*-(3-chloro-2,4-difluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: ^1H NMR (400

MHz, d_6-DMSO): 8.81 (d, 1H), 8.39 (d, 1H), 7.61 (m, 1H), 7.47 (m, 1H), 7.42 (s, 1H), 4.17 (m, 2), 4.02 (s, 3H), 3.67 (m, 1H), 3.05 (m, 2H), 2.91-2.75 (m, 5H), 2.34 (m, 1H), 2.16 (m, 2H), 1.75 (m, 1H), 1.57 (m, 2H), 1.35 (m, 1H). MS (EI) for $C_{24}H_{25}N_4O_2F_2Cl$: 475 (M^+).

Example 14

***N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride:**

[0199] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: A solution of 4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetate (salt) (0.22 g, 0.47 mmol), 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (0.16 g, 0.51 mmol), K_2CO_3 (0.33 g, 2.36 mmol) in N,N-dimethylacetamide (5 mL) was heated in a sealed reaction tube at 90°C for 12 h. The crude reaction mixture was diluted with 100 mL 10% methanol in ethyl acetate and washed with saturated aqueous sodium bicarbonate (1x 30 mL), water (1 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 3:2 hexanes:acetone) provided 1,1-dimethylethyl (3a*R*,6a*S*)-5-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta-[*c*]pyrrole-2(1*H*)-carboxylate which was used directly in the next step. MS (EI) for $C_{28}H_{31}Cl_2FN_4O_4$: 577, 579 (MH^+).

[0200] *N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclo-penta[*c*]pyrrol-5-yl]methyl]oxy}quinazolin-4-amine hydrochloride: 1,1-Dimethylethyl (3a*R*,6a*S*)-5-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-oxy}methyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was taken up in methanol (10 mL) and treated with 4.0M hydrogen chloride in dioxane (excess) and heated briefly to reflux. Concentration *in vacuo* provided *N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-yl]methyl]oxy}quinazolin-4-amine hydro-chloride. MS (EI) for $C_{28}H_{31}Cl_2FN_4O_4$: 477, 479 (MH^+).

[0201] *N*-(3,4-Dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclo-penta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: *N*-(3,4-

Dichloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-yl]methyl]oxy}quinazolin-4-amine hydrochloride was solubilized in formic acid (5.0 mL) and 37% aqueous formaldehyde (1 mL) was added. The solution was heated to 95°C for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was taken up in a mixture of 10% methanol in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (2x 30 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered then concentrated and purified by HPLC (reverse-phase, water/acetonitrile/0.1% TFA). Upon removal of solvent the product was taken up in 10% methanol in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (2x 30 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated then taken up in methanol and treated with 4.0 M hydrogen chloride in dioxane (1eq.). Removal of solvent *in vacuo* provided 78.3 mg (25%) of *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride. ^{1}H NMR (400 MHz, d_6-DMSO): 11.00 (bs, 1H), 8.36 (d, 1H), 8.10 (s, 1H), 7.58 (s, 2H), 7.20 (d, 1H), 4.16 (m, 2H), 4.00 (s, 3H), 3.35 (bs, 3H), 2.50 (m, 2H), 2.21 (m, 3H), 2.03 (m, 2H), 1.60 (m, 2H), 1.12 (m, 2H). MS (EI) for $C_{24}H_{25}Cl_2FN_4O_2$: 491, 493 (MH^+).

[0202] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0203] *N*-(4,5-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 10.9 (bs, 1H), 8.46 (d, 1H), 8.10 (s, 1H), 8.04 (s, 1H), 7.93 (s, 1H), 7.54 (s, 1H), 4.18 (m, 2H), 4.01 (s, 3H), 3.33 (bs, 3H), 2.46 (m, 2H), 2.23 (s, 3H), 2.04 (m, 2H), 1.58 (m, 2H), 1.14 (m, 2H). MS (EI) for $C_{24}H_{25}Cl_2FN_4O_2$: 491 (MH^+).

[0204] *N*-(4-bromo-2,3-dichlorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 11.0 (bs, 1H), 8.60 (s, 1H), 8.14 (s, 1H), 7.76 (d, 1H), 7.44 (t, 1H), 7.24 (s, 1H), 4.16 (m, 2H), 4.00 (s, 3H), 3.35 (bs, 3H), 2.50 (m, 2H), 2.18 (m, 3H), 2.03 (m, 2H), 1.60 (m, 2H), 1.12 (m, 2H). MS (EI) for $C_{24}H_{25}BrCl_2N_4O_2$: 550, 552 (MH^+).

[0205] *N*-(3,4-dichlorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-

DMSO): 10.98 (bs, 1H), 8.88 (s, 1H), 8.41 (s, 1H), 8.20 (d, 1H), 7.86 (d, 1H), 7.75 (s, 1H), 7.46 (s, 1H), 4.08 (m, 2H), 3.98 (s, 3H), 3.28 (m, 2H), 2.54 (m, 2H), 2.20 (s,m, 4H), 2.18 (m, 2H), 1.62 (m, 2H), 1.24 (m, 2H). MS (EI) for $C_{24}H_{26}Cl_2N_4O_2$: 473 (MH^+).

Example 15

***N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-(1-methylethyl)octahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride**

[0206] *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-(1-methylethyl)octahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: A solution of *N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine hydrobromide (0.1 g, 0.166 mmol), acetone (0.024 mL, 0.332 mmol), and glacial acetic acid (5 drops) in acetonitrile:water (3:1) was cooled to 0°C and sodium triacetoxyborohydride (53.0 mg, 0.249 mmol) was added. The solution was warmed to room temperature and stirred 12 h. Additional acetic acid (5 drops), acetone (0.30 mL, 6.54 mmol), sodium triacetoxyborohydride (0.300 g, 1.42 mmol) was added in portions over 12 h. The acetonitrile was removed *in vacuo* and the aqueous layer was diluted with saturated aqueous sodium bicarbonate and 10% methanol in ethyl acetate then the layers were separated. The aqueous layer was extracted with 10% methanol in ethyl acetate (2 x 75 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography (SiO_2, gradient of 30-50% methanol in chloroform) followed by concentration and treatment in methanol with 4.0 M hydrogen chloride in dioxane (0.05 mL) and concentration provided *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-(1-methylethyl)octahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride (75.7 mg, 76% yield). ^{1}H NMR (400 MHz, d_4-MeOH): 8.69 (s, 1H), 7.97 (s, 1H), 7.67 (d, 1H), 7.50 (t, 1H), 7.28 (s, 1H), 4.27 (d, 2H), 4.07 (s, 3H), 3.84-3.20 (m, 4H), 3.01 (m, 3H), 2.80 (m, 1H) 2.34 (m, 3H), 1.52 (m, 2H), 1.42 (dd, 6H); MS (EI) for $C_{26}H_{29}N_4O_2FClBr$: 565 (MH^+).

[0207] Using the same synthetic techniques and/or substituting with alternative reagents, the following compound of the invention was also prepared.

[0208] *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-(1-methylethyl)octahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.68 (broad s, 1H), 7.98 (broad s, 1H), 7.54 (m, 3H), 7.32 (broad s, 1H), 4.27 (d, 2H), 4.07 (s, 3H), 3.84-3.20 (m, 4H), 3.01 (m, 3H), 2.80 (m, 1H) 2.34 (m, 3H), 1.93-1.75 (m, 2H), 1.42 (dd, 6H); MS (EI) for $C_{26}H_{29}N_4O_2FCl_2$: 519 (MH^+).

Example 16

_N_-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-ethyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride

[0209] *N*-(4-Bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-ethyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: A solution of *N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine hydrobromide (0.1 g, 0.166 mmol) and acetaldehyde (0.010 mL, 0.249 mmol) in 50% methanol in tetrahydrofuran was cooled to 0°C and sodium cyanoborohydride (1 M in THF, 0.10 mL, 0.200 mmol) was added. The solution was warmed to room temperature and stirred for 1.5 h. The solvents were removed and the residue was partitioned between water and 10% methanol in ethyl acetate. The layers were separated and the aqueous layer was extracted with 10% methanol in ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography (SiO_2, gradient of 5-10% methanol in chloroform), followed by treatment in methanol with 4.0 M hydrogen chloride in dioxane (0.05 mL) and concentration provided *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-ethyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy) quinazolin-4-amine hydrochloride (37.5 mg, 36% yield). ^{1}H NMR (400 MHz, d_6-DMSO): 8.75 (d, 1H), 8.21 (broad s, 1H), 7.75 (d, 3H), 7.54 (t, 1H), 7.34 (m, 1H), 7.12 (d, 1H), 4.16 (d, 2H), 4.00 (s, 3H), 3.75 (m, 1H), 3.11-2.65 (m, 3H), 2.40 (m, 1H), 2.15 (m, 2H), 1.61 (m, 2H), 1.26 (m, 5); MS (EI) for $C_{25}H_{27}N_4O_2FClBr$: 551 (MH^+).

[0210] Using the same synthetic techniques and/or substituting with alternative reagents, the following compound of the invention were prepared:

[0211] *N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3a*R*,5*r*,6a*S*)-2-(2-methylpropyl)octahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine

hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 8.73 (d, 1H), 8.32 (broad s, 1H), 7.76 (d, 1H), 7.54 (t, 1H), 7.41 (m, 1H), 7.22 (d, 1H), 4.18 (d, 2H), 4.01 (s, 3H), 3.74 (m, 1H), 3.11 (m, 1H), 2.94 (m, 5H), 2.65 (m, 1H), 2.40 (m, 1H), 2.13 (m, 2H), 2.00 (m, 1H), 1.69 (m, 1H), 1.36 (m, 1H), 0.98 (t, 6H); MS (EI) for $C_{27}H_{31}N_4O_2FClBr$: 579 (MH^+).

[0212] *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-ethyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 8.77 (d, 1H), 8.36 (broad s, 1H), 7.63 (m, 2H), 7.42 (m, 1H), 7.20 (d, 1H), 4.17 (d, 2H), 4.02 (s, 3H), 3.74 (m, 1H), 3.11-2.75 (m, 4H), 2.66 (m, 1H), 2.36 (m, 1H), 2.14 (m, 2H), 1.80 (m, 1H), 1.65 (m, 1H), 1.28 (m, 5H); MS (EI) for $C_{25}H_{27}N_4O_2FCl_2$: 505 (MH^+).

[0213] *N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3a*R*,5*r*,6a*S*)-2-(2-methylpropyl)octahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 8.83 (d, 1H), 8.36 (d, 1H), 7.68 (d, 1H), 7.62 (t, 1H), 7.43 (d, 1H), 7.30 (d, 1H), 4.18 (d, 2H), 4.01 (s, 3H), 3.75 (m, 1H), 3.11 (m, 1H), 2.95 (m, 5H), 2.67 (m, 1H), 2.40 (m, 1H), 2.14 (m, 2H), 2.00 (m, 1H), 1.69 (m, 1H), 1.36 (m, 1H), 0.98 (t, 6H); MS (EI) for $C_{27}H_{31}N_4O_2FCl_2$: 533 (MH^+).

Example 17

Ethyl (3a*R*,6a*S*)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy) quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate hydrochloride

[0214] Ethyl (3a*R*,6a*S*)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy) quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate hydrochloride: A solution of *N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine hydrobromide (0.050 g, 0.0830 mmol), triethylamine (0.046 mL, 0.0332 mmol) in 2.0 mL dichloromethane was cooled to 0°C and ethyl chloridocarbonate (0.010 mL, 0.0913 mmol) was added. The solution was stirred for 0.5 h at low temperature and quenched with saturated aqueous sodium bicarbonate. The reaction mixture was then partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 75 mL). The combined organic

layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 5% methanol in dichloromethane), followed by treatment in methanol with 4.0 M hydrogen chloride in dioxane (0.05 mL) and concentration provided ethyl (3a*R*,6a*S*)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate hydrochloride (27.7 mg, 53% yield). ^{1}H NMR (400 MHz, d_4-MeOH): 8.59 (s, 1H), 7.83 (s, 1H), 7.60 (d, 1H), 7.41 (t, 1H), 7.12 (s, 1H), 4.14 (d, 2H), 4.11 (m, 2H), 4.09 (s, 3H), 3.45 (dd, 2H), 3.30 (dd, 2H), 2.67 (m, 2H), 2.58 (m, 1H), 2.12 (m, 2H), 1.74 (m, 1H), 1.36 (m, 2H), 1.18 (t, 3H); MS (EI) for $C_{26}H_{27}N_4O_4FClBr$: 595 (MH^+).

[0215] Using the same synthetic techniques and/or substituting with alternative reagents, the following compound of the invention were prepared:

[0216] *N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3a*R*,5*r*,6a*S*)-2-(methylsulfonyl)octahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.70 (s, 1H), 7.94 (s, 1H), 7.69 (d, 1H), 7.49 (t, 1H), 7.23 (s, 1H), 4.24 (d, 2H), 4.18 (m, 2H), 4.09 (s, 3H), 3.45 (dd, 2H), 2.90 (s, 3H), 2.87 (m, 3H), 2.59 (m, 1H), 2.28 (m, 2H), 1.43 (m, 2H); MS (EI) for $C_{24}H_{25}N_4O_4FSClBr$: 601 (MH^+).

[0217] 7-({[(3a*R*,5*r*,6a*S*)-2-acetyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-*N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.70 (s, 1H), 7.97 (s, 1H), 7.69 (d, 1H), 7.49 (t, 1H), 7.28 (s, 1H), 4.14 (d, 2H), 4.25 (m, 2H), 4.08 (s, 3H), 3.31 (m, 1H), 3.02 (m, 4H), 2.78 (m, 2H), 2.36 (m, 1H), 1.93 (m, 3H), 1.43 (m, 2H); MS (EI) for $C_{25}H_{25}N_4O_3FClBr$: 565 (MH^+).

Example 18

N-(3,4-dichlorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride:

[0218] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate: Sodium borohydride (0.15 g, 4.00 mmol), was added to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-oxo-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.45 g, 2.00 mmol) in 10 mL methanol at 0°C and the reaction mixture was stirred for 1 h at this temperature. The solvent was evaporated, the crude mixture was diluted with 100 mL ethyl

acetate and washed with water (30 mL), 1M aqueous hydrochloric acid and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44g, 98%). ^{1}H NMR (400 MHz, d_6-DMSO): 4.08 (m, 1H), 3.40 (m, 2H), 3.30 (m, 2H), 2.50 (m, 2H), 1.98 (m, 2H), 1.40 (s, 9H), 1.30 (m, 2H). MS (EI) for $C_{12}H_{21}NO_3$: 228 (MH^+).

[0219] 1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: Methanesulfonyl chloride (0.18 mL, 2.33 mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44 g, 1.94 mmol) and triethylamine (0.81 mL, 5.81 mmol) in 10 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{13}H_{23}NO_5S$: 306 (MH^+).

[0220] 1,1-dimethylethyl (3a*R*,6a*S*)-5-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy) quinazolin-7-yl]oxy})hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: A solution of 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetate (salt) (0.22 g, 0.49mmol), 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (0.15 g, 0.45 mmol), potassium carbonate (0.34 g, 2.50 mmol) in N,N-dimethylacetamide (5 mL) was heated in a sealed reaction tube at 90°C for 12 h. The crude reaction mixture was diluted with 100 mL 10% methanol in ethyl acetate and washed with saturated aqueous sodium bicarbonate (1x 30 mL), water (1 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography (SiO_2, 3:2 hexanes:acetone) provided 1,1-dimethylethyl (3a*R*,6a*S*)-5-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy})hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (0.23 g, 98%). ^{1}H NMR (400 MHz, d_6-DMSO): 9.57 (s, 1H), 8.52 (s, 1H), 8.24 (d, 1H), 7.88 (dd, 1H), 7.78 (s, 1H), 7.62 (d, 1H), 7.13 (s, 1H), 5.15 (m, 1H), 3.96 (s, 3H), 3.42 (m, 2H), 3.36 (m, 2H), 2.80 (bs, 2H), 2.06 (m, 2H), 1.94 (m, 2H), 1.40 (s, 9H). MS (EI) for $C_{27}H_{30}Cl_2N_4O_4$: 547 (MH^+).

[0221] *N*-(3,4-dichloro-phenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-yl]oxy} quinazolin-4-amine hydrochloride: 1,1-Dimethylethyl (3a*R*,6a*S*)-5-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy})hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (0.23 g, 0.42 mmol) was taken up in methanol (10 mL) and treated with 4.0M hydrogen chloride in dioxane (excess) and heated briefly to reflux. Concentration *in vacuo* provided *N*-(3,4-dichloro-phenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta[*c*]pyrrol-5-yl]oxy} quinazolin-4-amine hydrochloride (0.20 g, 100%). MS (EI) for $C_{22}H_{22}Cl_2N_4O_2$: 445 (MH^+).

[0222] *N*-(3,4-Dichlorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: *N*-(3,4-Dichloro-phenyl)-6-(methyloxy)-7-{[(3a*R*,5*r*,6a*S*)-octahydrocyclopenta-[*c*]pyrrol-5-yl]oxy}quinazolin-4-amine hydrochloride (0.20 g, 0.42 mmol) was solubilized in formic acid (5.0 mL) and 37% aqueous formaldehyde (1 mL) was added. The solution was heated to 95°C for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was taken up in a mixture of 10% methanol in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (2x 30 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by HPLC (reverse-phase, acetonitrile/water/0.1% TFA). Upon removal of solvent the product was taken up in a mixture of 10% methanol in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (2x 30 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated then the product was taken up in methanol and treated with 4.0 M hydrogen chloride in dioxane (1eq.). Removal of solvent *in vacuo* provided 116 mg (56%) of *N*-(3,4-dichlorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride. ^{1}H NMR (400 MHz, d_6-DMSO): 11.05 (bs, 1H), 8.90 (s, 1H), 8.44 (s, 1H), 8.18 (d, 1H), 7.84 (dd, 1H), 7.76 (s, 1H), 7.48 (s, 1H), 5.30 (m, 1H), 4.00 (s, 3H), 3.35 (m, 2H), 2.90 (m, 2H), 2.24 (m, 5H), 2.10 (m, 2H), 1.24 (m, 2H). MS (EI) for $C_{23}H_{24}Cl_2N_4O_2$: 459, 461 (MH^+).

Example 19

N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride

[0223] 3-(Chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: A solution of (3*R*)-morpholin-3-ylmethanol (4.21 g, 36.0 mmol) in 2-(chloromethyl)oxirane (28.2 mL, 0.360 mol) was heated to 40°C for 3 h and then the solution was concentrated *in vacuo*. The intermediate was cooled in an ice bath and treated with 30.0 mL of concentrated sulfuric acid. The mixture was heated to 170°C for 2 h and then allowed to cool to room temperature. The mixture was poured into ice-water and solid sodium bicarbonate was carefully added until the solution was basic. 10% methanol in ethyl acetate was added and the biphasic mixture was filtered. The layers were separated and the aqueous layer was extracted (3 x 100 mL 10% methanol in ethyl acetate). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 2:5 hexanes:ethyl acetate) provided 3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine 2.44g (35%) as two separated diastereomers. (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (0.886 g, 13% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.91 (m, 3H), 3.82 (m, 1H), 3.68 (dt, 1H), 3.61 (dd, 1H), 3.47 (dd, 1H), 3.35 (t, 1H), 3.19 (t, 1H), 2.80 (d, 1H), 2.54 (m, 2H), 2.40 (m, 2H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 (MH^+). (3*S*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (1.55 g, 22% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.85 (m, 2H), 3.73 (m, 3H), 3.50 (m, 2H), 3.29 (t, 1H), 3.18 (t, 1H), 2.85 (dd, 1H), 2.64 (dd, 1H), 2.40 (m, 2H), 2.17 (t, 1H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 (MH^+).

[0224] Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: A suspension of (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine (1.97 g, 10.3 mmol) and potassium acetate (10.1 g, 102 mmol) in DMF (20.0 mL) was stirred at 140°C for 16 h, and then at 150°C for another 12 h. The reaction mixture was partitioned between water (250 mL) and ethyl acetate (250 mL), the organic layer was washed with 5% lithium chloride (2 x 100 mL) and brine (100 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Column chromatography (SiO_2, 1:1 hexane:ethyl acetate, then 100% ethyl acetate) afforded 0.92 g (42%) of hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate as a yellow oil. Distinct diastereomers as described above were converted in this step to give: (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): 4.18 (dd, 1H), 4.00 (m, 1H), 3.80 (dd, 1H), 3.68 (dt, 1H), 3.60 (dd, 1H), 3.46 (m, 2H), 3.22 (t, 1H), 2.64 (dd, 1H), 2.53 (m, 2H), 2.43-2.35 (m,

2H), 2.10 (s, 3H), and (3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): 4.09 (d, 2H), 3.90-3.82 (m, 2H), 3.75-3.64 (m, 3H), 3.27 (t, 1H), 3.18 (t, 1H), 2.69 (dd, 1H), 2.63 (m, 1H), 2.46-2.33 (m, 2H), 2.16 (t, 1H), 2.10 (s, 3H).

[0225] (3*R*,9a*S*)-Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate: To a solution of (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate (0.922 g, 4.28 mmol) in methanol (14.0 mL) was added 1.03 mL (4.50 mmol) of sodium methoxide (25% wt. in methanol) dropwise at room temperature. After 5 min., 1.6 mL (6.43 mmol) of 4.0M hydrogen chloride in dioxane was added and a pink precipitate formed. The solution was concentrated *in vacuo* and the pink solid was taken up in 30.0 mL dichloromethane. This slurry was cooled in an ice bath and triethylamine (3.0 mL, 21.5 mmol) was added, followed by methanesulfonyl chloride (0.37 mL, 4.71 mmol). The resultant yellow solution was stirred for 30 minutes at room temperature. The mixture was then partitioned between dichloromethane and saturated aqueous sodium bicarbonate then the aqueous layer was extracted (3 x 50 mL dichloromethane). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide crude (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate which was taken on to the following reaction without purification.

[0226] *N*-(4-Bromo-3-chloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: A solution of (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate (0.215 g, 0.856 mmol), 4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-ol hydrochloride (0.247 g, 0.570 mmol), and potassium carbonate (0.400 g, 2.90 mmol) in DMF (1.9 mL) was heated in a sealed reaction tube at 75°C for 12 h, then 90°C for 12 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between 10% methanol in ethyl acetate and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted (3 x 50 mL 10% methanol in ethyl acetate). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by HPLC (reverse-phase, acetonitrile/water/0.1% TFA). Upon removal of solvent the product was taken up in methanol and treated with Bio-Rad AG 1-X8 resin (hydroxide form) until pH 8.

The product was filtered and concentrated *in vacuo* then taken up in methanol and treated with 4.0 M hydrogen chloride in dioxane (0.10 mL). Removal of solvent *in vacuo* provided 32.1 mg (10%) of *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride. MS (EI) for $C_{23}H_{23}N_4O_4FClBr$: 554 (M^+).

[0227] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0228] *N*-(3,4-dichlorophenyl)-7-[(hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl)oxy]-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 8.90 (s, 1H), 8.50 (s, 1H), 8.19 (d, 1H), 7.85 (d, 1H), 7.75 (d, 1H), 7.42 (s, 1H), 4.51 (m, 1H), 4.32 (m, 2H), 4.04 (s, 3H), 4.00-3.62 (m, 4H); MS (EI) for $C_{23}H_{24}N_4O_4Cl_2B$: 491 (MH^+).

[0229] *N*-(3,4-dichloro-2-fluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.71 (s, 1H), 7.99 (s, 1H), 7.58-7.52 (m, 2H), 7.33 (s, 1H), 4.50 (m, 1H), 4.44 (d, 2H), 4.17-3.94 (m, 4H), 4.09 (s, 3H), 3.82-3.59 (m, 5H), 3.54-3.37 (m, 2H); MS (EI) for $C_{23}H_{23}N_4O_4Cl_2F$: 509 (MH^+).

[0230] *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.71 (s, 1H), 7.99 (s, 1H), 7.69 (d, 1H), 7.49 (t, 1H), 7.32 (s, 1H), 4.49 (m, 1H), 4.44 (m, 2H), 4.16-3.95 (m, 4H), 4.10 (s, 3H), 3.82-3.58 (m, 5H), 3.54-3.35 (m, 2H); MS (EI) for $C_{23}H_{23}N_4O_4BrClF$: 553 (MH^+).

[0231] *N*-(3-chloro-2,4-difluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: MS (EI) for $C_{23}H_{23}N_4O_4ClF_2$: 493 (MH^+).

[0232] *N*-(4,5-dichloro-2-fluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.73 (s, 1H), 7.99 (s, 1H), 7.86 (d, 1H), 7.64 (d, 1H), 7.33 (s, 1H), 4.51 (m, 1H), 4.44 (d, 2H), 4.16-3.94 (m, 4H), 4.10 (s, 3H), 3.84-3.60 (m, 5H), 3.54-3.36 (m, 2H); MS (EI) for $C_{23}H_{23}N_4O_4ClF_2$: 509 (MH^+).

[0233] *N*-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.73 (s, 1H), 7.98 (s, 1H), 7.85 (d, 1H), 7.76 (d, 1H), 7.33 (s, 1H), 4.49 (m, 1H), 4.44 (d, 2H), 4.16-3.94 (m, 4H), 4.09 (s, 3H), 3.82-3.60 (m, 5H), 3.53-3.35 (m, 2H); MS (EI) for $C_{23}H_{23}N_4O_4BrClF$: 553 (MH^+).

[0234] *N*-(4-bromo-2,3-dichlorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.67 (s, 1H), 8.00 (s, 1H), 7.84 (d, 1H), 7.48 (d, 1H), 7.34 (s, 1H), 4.51 (m, 1H), 4.44 (d, 2H), 4.09 (s, 3H), 4.15-4.00 (m, 4H), 3.82-3.63 (m, 5H), 3.63-3.38 (m, 2H); MS (EI) for $C_{23}H_{23}N_4O_4Cl_2Br$: 570 (MH^+).

[0235] *N*-(4-bromo-2,3-dichlorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: MS (EI) for $C_{23}H_{23}N_4O_4Cl_2Br$: 570 (MH^+).

[0236] *N*-(3,4-dichloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: MS (EI) for $C_{23}H_{23}N_4O_4FCl_2$: 509 (MH^+).

[0237] *N*-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: MS (EI) for $C_{23}H_{23}N_4O_4FClBr$: 554 (MH^+).

[0238] *N*-(4,5-dichloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.74 (s, 1H), 8.00 (s, 1H), 7.86 (d, 1H), 7.64 (d, 1H), 7.35 (broad s, 1H), 4.51 (m, 2H), 4.44 (m, 1H), 4.25-3.95 (m, 4H), 4.09 (s, 3H), 3.82-3.63 (m, 5H), 3.63-3.38 (m, 2H); MS (EI) for $C_{23}H_{23}N_4O_4FCl_2$: 509 (MH^+).

[0239] *N*-(3-chloro-2,4-difluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: MS (EI) for $C_{23}H_{23}N_4O_4F_2Cl$: 493 (MH^+).

Example 20

***N*-(3,4-dichlorophenyl)-7-[(2-{[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}ethyl)oxy]-6-(methyloxy)quinazolin-4-amine**

[0240] 7-[(2-Aminoethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine hydrochloride: A solution of 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetate (salt) (1.00 g, 2.15 mmol), 1,1-dimethylethyl (2-bromoethyl)carbamate (0.480 g, 2.15 mmol), and potassium carbonate (1.78 g, 12.9 mmol) in N,N-dimethylacetamide (2.2 mL) was heated to 100°C for 2.5 h. An additional 0.23 g (1.03 mmol) of 1,1-dimethylethyl (2-bromoethyl)carbamate was added and the reaction mixture was further heated to 100°C for a total of 7 h. The crude reaction mixture was partitioned between water and ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, 3:2 hexanes:acetone) gave N-Boc product, which was then taken up in methanol and treated with 4M hydrogen chloride in dioxane while heating. Dilution with ethyl ether precipitated a pale yellow solid, which was collected by filtration and dried to give 0.761 g (94%) of 7-[(2-aminoethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine hydrochloride. ^{1}H NMR (400 MHz, d_6-DMSO): 12.01 (s, 1H), 8.94 (s, 1H), 8.67 (s, 1H), 8.35 (broad s, 2H), 8.21 (s, 1H), 7.90 (dd, 1H), 7.75 (d, 1H), 7.53 (s, 1H), 4.43 (t, 2H), 4.08 (s, 3H), 3.36 (m, 2H).

[0241] *N*-(3,4-Dichlorophenyl)-7-[(2-{[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl] amino}ethyl)oxy]-6-(methyloxy)quinazolin-4-amine: To a DMF solution (3.0 mL) of 7-[(2-aminoethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine hydrochloride (56.8 mg, 0.137 mmol) at room temperature, was added glacial acetic acid (3 drops), (1*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-one (49.0 mg, 0.137 mmol), and sodium triacetoxyborohydride (43.0 mg, 0.205 mmol). After stirring for 12 h, additional (1*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-one (50.0 mg, 0.140 mmol), acetic acid (3 drops) and sodium triacetoxyborohydride were added. The solution was quenched with water, filtered and purified by HPLC (reverse-phase, acetonitrile/water/0.1% TFA). Upon removal of solvent, the product was taken up in methanol and treated with Bio-Rad AG 1-X8 resin (hydroxide form) until pH 8. The product was filtered and concentrated *in vacuo*, to provide 45.1 mg (66%) of *N*-(3,4-dichlorophenyl)-7-[(2-{[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}ethyl)oxy]-6-(methyloxy)quinazolin-4-amine. ^{1}H NMR (400 MHz, d_6-DMSO): 9.63 (s, 1H), 8.55 (s, 1H), 8.26 (d, 1H), 7.90 (dd, 1H), 7.83 (s, 1H), 7.65 (s, 1H), 7.23 (d,

1H), 4.20 (t, 1H), 4.15 (t, 3H), 3.97 (s, 1H), 3.03 (m, 1H), 2.91 (t, 2H), 2.81 (t, 1H), 2.17 (s, 3H), 2.00-1.84 (m, 6H), 1.67-1.32 (m, 4H); MS (EI) for $C_{25}H_{29}N_5O_2Cl_2$: 502 (MH^+).

Example 21

***N*-(3,4-dichlorophenyl)-7-{[(3-*exo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride**

[0242] *N*-(3,4-Dichlorophenyl)-7-{[(3-*exo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride: A solution of 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetate (salt) (0.150 g, 0.322 mmol), (3-*endo*)-3-[(methylsulfonyl)methyl]-8-azabicyclo[3.2.1]octane (0.106 g, 0.483 mmol), and potassium carbonate (0.220 g, 1.60 mmol) in N,N-dimethylacetamide (1.1 mL) was heated in a sealed tube at 100°C for 12 h, followed by 48 h at room temperature. The crude reaction mixture was filtered through celite using methanol eluent, and the solvents were removed *in vacuo*. The residue was purified by HPLC (reverse-phase, acetonitrile/water/0.1% TFA). Upon removal of solvent, the product was taken up in methanol and treated with Bio-Rad AG 1-X8 resin (hydroxide form) until pH 8. The product was filtered and concentrated *in vacuo*, then taken up in methanol and treated with 4.0 M hydrogen chloride in dioxane (0.050 mL). Removal of solvent *in vacuo* provided 48.7 mg (31%) of *N*-(3,4-dichlorophenyl)-7-{[(3-*exo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]oxy}-6-(methyloxy)quinazolin-4-amine hydrochloride. ^{1}H NMR (400 MHz, d_6-DMSO): 10.69 (s, 1H), 8.92 (s, 1H), 8.32 (s, 1H), 8.17 (d, 1H), 7.81 (m, 2H), 7.75 (d, 1H), 5.05 (m, 1H), 4.02 (s, 3H), 2.69 (d, 2H), 2.39 (m, 1H), 2.29-2.18 (m, 6H); MS (EI) for $C_{23}H_{24}N_4O_2Cl_2$: 459 (MH^+).

Example 22

***N*-(3,4-dichlorophenyl)-7-({[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride**

[0243] 7-{[(3-*endo*)-8-Azabicyclo[3.2.1]oct-3-ylmethyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine hydrochloride: A solution of 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetate (salt) (0.200 g, 0.429 mmol), 1,1-dimethylethyl (3-*endo*)-3-{[(methylsulfonyl)oxy]methyl}-8-azabicyclo[3.2.1]octane-8-carboxylate (0.200 g, 0.626 mmol), and potassium carbonate (0.300 g, 2.17 mmol) in N,N-

dimethylacetamide (1.4 mL) was heated in a sealed tube at 110°C for 12 h. Additional mesylate (0.430 g, 1.35 mmol) was added and the mixture was heated for 2 h at 110°C. The crude reaction mixture was partitioned between 10% methanol in ethyl acetate (50 mL) and water (50 mL). The layers were separated and the organic layer was washed with water (2 x 50 mL) and 1M aqueous sodium hydroxide (1 x 50 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO_2, 2:1 hexanes:ethyl acetate), followed by HPLC (reverse-phase, acetnitrile/water/0.1% TFA). Solvent was removed *in vacuo* and the residue partitioned with 10% methanol in ethyl acetate and water. The aqueous layer was made basic with saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was further extracted with 10% methanol in ethyl acetate (2x). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and the concentrated *in vacuo*. The residue was taken up in methanol and treated with 4.0 M hydrogen chloride in dioxane then concentrated to provide 7-{[(3-*endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine hydrochloride (0.104 g, 53%). MS (EI) for $C_{23}H_{24}N_4O_2Cl_2$: 459 (MH^+).

[0244] *N*-(3,4-Dichlorophenyl)-7-({[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: 7-{[(3-*Endo*)-8-azabicyclo[3.2.1]oct-3-ylmethyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine hydrochloride, (0.104 g, 0.210 mmol) was combined with 37% aqueous formaldehyde (0.10 mL, 1.26 mmol) in formic acid (1.0 mL) and the solution was heated to 110°C for 12 h. The solvent was removed *in vacuo* and the residue was taken up in methanol and treated with Bio-Rad AG 1-X8 resin (hydroxide form) until pH 8. The product was filtered and concentrated *in vacuo*. The residue was purified by HPLC (reverse-phase, acetonitrile/water/0.1% TFA). Upon removal of solvent, the product was taken up in methanol and treated with Bio-Rad AG 1-X8 resin (hydroxide form) until pH 8. The product was filtered and concentrated *in vacuo*, then taken up in methanol and treated with 4.0 M hydrogen chloride in dioxane (0.10 mL). Removal of solvent *in vacuo* provided 41.4 mg (39%) of *N*-(3,4-dichlorophenyl)-7-({[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride. ^1H NMR (400 MHz, d_6-DMSO): 8.89 (s, 2H), 8.45 (s, 1H), 8.20 (s, 1H), 7.86 (d, 1H), 7.75 (d, 1H), 7.46 (s, 1H),

4.24 (m, 2H), 4.04 (s, 3H), 3.97 (broad s, 1H), 3.85 (broad s, 1H), 2.65 (d, 1H), 2.25-2.51 (m, 6H), 2.03-1.80 (m, 5H); MS (EI) for $C_{24}H_{26}N_4O_2Cl_2$: 473 (MH^+).

Example 23

***N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(8a*R*)-tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazin-6-ylmethyl]oxy}quinazolin-4-amine trifluoroacetate**

[0245] (8a*R*)-6-(Chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine: A solution of (4*R*)-1,3-thiazolidin-4-ylmethanol (0.300 g, 2.52 mmol) in 2-(chloromethyl)oxirane (2.0 mL, 25.5 mmol) was heated under nitrogen to 40°C for 12 h. The solution was then cooled to room temperature and 2-(chloromethyl)oxirane was removed *in vacuo*. The crude intermediate was cooled in ice, and was taken up in 2.0 mL of concentrated sulfuric acid. The resulting mixture was heated to 200°C for 0.5 h then poured carefully onto wet ice, which was allowed to melt. The aqueous solution was carefully made basic using solid sodium bicarbonate and the resulting mixture was filtered using water and 10% methanol in ethyl acetate as eluent. The layers were separated and the aqueous layer was extracted with 10% methanol in ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 11.6 mg (2.4% yield) of crude (8a*R*)-6-(chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine as a mixture of diastereomers which was directly taken on to the next step.

[0246] *N*-(3,4-Dichlorophenyl)-6-(methyloxy)-7-{[(8a*R*)-tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazin-6-ylmethyl]oxy}quinazolin-4-amine trifluoroacetate: A solution of (8a*R*)-6-(chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine (11.6 mg, 0.0599 mmol), 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetate (salt) (30.0 mg, 0.0644 mmol), and potassium carbonate (45.0 mg, 0.326 mmol) in N,N-dimethylacetamide (1.0 mL) was heated in a sealed tube to 150°C for 12 h. The crude reaction mixture was directly purified via reverse-phase preparative HPLC (acetonitrile/water/0.1% TFA). Lyophillization of the pure fractions yielded 3.5 mg (8.9%) of *N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(8a*R*)-tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazin-6-ylmethyl]oxy} quinazolin-4-amine trifluoroacetate. ^{1}H NMR (400 MHz, d_6-DMSO): 8.80 (s, 1H), 8.11 (s, 1H), 7.99 (s, 1H), 7.74 (s, 2H), 7.29 (s, 1H), 4.29 (d, 2H), 4.11 (m, 2H), 4.00 (s, 3H), 3.96

(m, 1H), 2.99 (m, 2H), 2.56 (t, 1H), 2.367 (m, 1H); MS (EI) for $C_{22}H_{22}N_4O_3SCl_2$: 492 (MH^+).

Example 24

***N*-(3,4-dichlorophenyl)-7-({2-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]ethyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride**

[0247] 1,1-Dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1] octane-8-carboxylate: To a solution of 1,1-dimethylethyl (3-*endo*)-3-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (30.3 mg, 1.19 mmol) in dichloromethane (4.0 mL), was added triethylamine (0.5 mL, 3.56 mmol) and the solution was cooled to 0°C under nitrogen. Methanesulfonyl chloride (0.11 mL, 1.42 mmol) was added slowly and mixture was allowed to warm to room temperature and stirred for 1h. The reaction mixture was partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 35.1 mg (89%) of 1,1-dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate, which was carried forward without purification.

[0248] 1,1-Dimethylethyl (3-*endo*)-3-(2-{[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}ethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate: To a solution of 1,1-dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate (0.175 g, 0.526 mmol) in N,N-dimethylacetamide (3.5 mL) was added 4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-ol trifluoroacetate (salt) (0.490 g, 1.05 mmol) and potassium carbonate (0.728 g, 5.26 mmol), and the reaction was stirred at 110°C for 18h. An additional portion of 1,1-dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate (0.175 g, 0.526 mmol) was added and the mixture was stirred at 140°C for 2h. Another portion of the mesylate (0.300 g, 1.05 mmol) in N,N-dimethylacetamide (4.0 mL) was added and the mixture continued to stir at 140°C for a further 18h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between 10% methanol in ethyl acetate and water. The organic layer was washed (3 x 50 mL water) and the combined aqueous portions were extracted (2 x 100 mL 10% methanol in ethyl acetate). All organic layers were combined,

dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by HPLC (reverse-phase, acetonitrile/water/0.1% TFA). Upon concentration the remaining aqueous layer was neutralized with solid sodium bicarbonate, extracted (100 mL 10% methanol in ethyl acetate), dried over anhydrous sodium sulfate then filtered and concentrated *in vacuo* to afford 1,1-dimethylethyl (3-*endo*)-3-(2-{[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}ethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (39.9 mg, 66% yield). ^{1}H NMR (400 MHz; d_6-DMSO): 9.43 (broad s, 1H), 8.48 (s, 1H), 7.87 (s, 1H), 7.61 (d, 1H), 7.53 (s, 1H), 7.22 (d, 1H), 7.02 (s, 1H), 4.23-3.82 (m, 4H), 3.80 (s, 3H), 2.19 (m, 1H), 1.93 (s, 6H), 1.69-1.42 (m, 3H), 1.36 (s, 9H), 1.22 (m, 1H).

[0249] 7-({2-[(3-*endo*)-8-Azabicyclo[3.2.1]oct-3-yl]ethyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine hydrochloride: 1,1-Dimethylethyl (3-*endo*)-3-(2-{[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}ethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate was solubilized in methanol (2.3 mL) and treated with 4.0 M hydrogen chloride in dioxane (2.3 mL). The solution was heated to reflux then immediately allowed to cool to room temperature. The solution was then concentrated *in vacuo* to give 7-({2-[(3-*endo*)-8-azabicyclo[3.2.1]oct-3-yl]ethyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy) quinazolin-4-amine hydrochloride (34.6 mg, 98% yield). MS (EI) for $C_{24}H_{26}Cl_2N_4O_2$: 473 (MH^+).

[0250] *N*-(3,4-Dichlorophenyl)-7-({2-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]ethyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride: To a solution of 7-({2-[(3-*endo*)-8-azabicyclo[3.2.1]oct-3-yl]ethyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy) quinazolin-4-amine hydrochloride (0.346 g, 0.678 mmol) in formic acid (2.7 mL), was added aqueous formaldehyde (37%, 0.27 mL, 4.07 mmol) and the mixture was heated to 110°C for 5h, then allowed to cool to room temperature. The solution was concentrated *in vacuo* and the residue was taken up in methanol and treated with AG 1-X8 resin (hydroxide form) to pH 8. The mixture was filtered and concentrated then the residue purified by HPLC (reverse-phase, acetonitrile/water/0.1% TFA) and the pure fractions lyophillized. The residue was taken up in methanol and neutralized with AG 1-X8 resin (hydroxide form) to pH 8 then filtered and concentrated. The residue was taken into methanol (3 mL) and treated with 4.0 M hydrogen chloride in dioxane to pH 2. Concentration *in vacuo* afforded the title

compound *N*-(3,4-dichlorophenyl)-7-({2-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]ethyl}oxy)-6-(methyloxy)quinazolin-4-amine hydrochloride (12.5 mg, 36% yield). ^{1}H NMR (400 MHz; d_6-DMSO): 8.86 (s, 2H), 8.40 (s, 1H), 8.16 (t, 1H), 7.82 (d, 1H), 7.73 (d, 1H), 7.38 (s, 1H). 4.22 (m, 2H), 4.03 (s, 3H), 3.92 (broad s, 2H), 2.28 (m, 2H), 2.12-1.91 (m, 6H)0, 1.88-1.58 (m, 6H); MS (EI) for $C_{25}H_{28}Cl_2N_4O_2$: 485 (MH^+).

Assays

[0251] For assay of activity, generally either an ephrin or a compound according to the invention is non-diffusably bound to an insoluble support having isolated sample-receiving areas (e.g., a microtiter plate, an array, etc.). The insoluble support may be made of any composition to which the compositions can be bound, is readily separated from soluble material, and is otherwise compatible with the overall method of screening. The surface of such supports may be solid or porous and of any convenient shape. Examples of suitable insoluble supports include microtiter plates, arrays, membranes and beads. These are typically made of glass, plastic (e.g., polystyrene), polysaccharides, nylon or nitrocellulose, Teflon™, etc. Microtiter plates and arrays are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples. The particular manner of binding of the composition is not crucial so long as it is compatible with the reagents and overall methods of the invention, maintains the activity of the composition and is nondiffusable. Exemplary methods of binding include the use of antibodies (which do not sterically block either the ligand binding site or activation sequence when the protein is bound to the support), direct binding to "sticky" or ionic supports, chemical crosslinking, the synthesis of the protein or agent on the surface, etc. Following binding of the protein or agent, excess unbound material is removed by washing. The sample receiving areas may then be blocked through incubation with bovine serum albumin (BSA), casein or other innocuous protein or other moiety.

[0252] One measure of inhibition is K_i. For compounds with IC_{50}'s less than 1 μM, the K_i or K_d is defined as the dissociation rate constant for the interaction of the agent with an ephrin. Exemplary compositions have K_i's of, for example, less than about 100 μM, less than about 10 μM, less than about 1 μM, and further for example having K_i's of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound is determined

from the IC_{50} based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (i.e., compound concentration) data are fitted to the equation:

[0253] Where V is the observed rate, V_{max}, is the rate of the free enzyme, I_0 is the inhibitor concentration, E_0 is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

[0254] Another measure of inhibition is GI_{50}, defined as the concentration of the compound that results in a decrease in the rate of cell growth by fifty percent. Exemplary compounds

$$V = V_{max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

have GI_{50}'s of, for example, less than about 1 mM, less than about 10 μM, less than about 1 μM, and further, for example, having GI_{50}'s of less than about 100 nM, still further having GI_{50}'s of less than about 10 nM. Measurement of GI_{50} is done using a cell proliferation assay.

[0255] Tyrosine kinase activity is determined by 1) measurement of kinase-dependent ATP consumption by in the presence of a generic substrate such as polyglutamine, tyrosine (pEY), by luciferase/luciferin-mediated chemiluminescence or; 2) incorporation of radioactive phosphate derived from ^{33}P-ATP into a generic substrate which has been adsorbed onto the well surface of polystyrene microtiter plates. Phosphorylated substrate products are quantified by scintillation spectrometry.

Structure Activity Relationships

[0256] Table 2 shows structure activity relationship data for selected compounds of the invention. Inhibition is indicated as IC_{50} with the following key: A = IC_{50} less than 50 nM, B = IC_{50} greater than 50 nM, but less than 1000 nM, C = IC_{50} greater than 1000 nM, but less than 20,000 nM, and D = IC_{50} greater than 20,000 nM. Abbreviations for enzymes listed in Table 2 are defined as follows: EphB4 and EphA2 refer to ephrin receptor tyrosine kinse family members ephrin B4 and A2; KDR, kinase insert domain receptor tyrosine kinase, and Flt-1, fms-like tyrosine kinase-1, are representative of the FLK family or receptor tyrosine

kinases; EGFR, epidermal growth factor receptor tyrosine kinase, and ErbB2 are representative of the HER family of receptor tyrosine kinases.

Table 2

#	Name	EphB4 IC_{50}	EphA2 IC_{50}	KDR IC_{50}	Flt-1 IC_{50}	EGFR IC_{50}	ErbB2 IC_{50}
1	N-(3,4-dichloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	A
2	N-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	A
3	N-(3-chloro-2,4-difluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	A
4	N-(4,5-dichloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	A
5	N-(4-bromo-5-chloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	A
6	N-(4-bromo-2,3-dichlorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine	A	A	A	C	A	B
7	N-(3,4-dichlorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	A
8	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	B	B	B	C	A	C
9	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	B	B	B	B	A	B

#	Name	EphB4 IC_{50}	EphA2 IC_{50}	KDR IC_{50}	Flt-1 IC_{50}	EGFR IC_{50}	ErbB2 IC_{50}
10	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	B	B	B	B	A	B
11	N-(3-chloro-2,4-difluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	B	B	B	B	A	B
12	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	A	A	A
13	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	A	A	A
14	N-(3-chloro-2,4-difluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	B	B	B	A	B
15	N-(3,4-dichlorophenyl)-7-[(hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl)oxy]-6-(methyloxy)quinazolin-4-amine	A	B	A	B	A	A
16	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	B	B	B	A	B
17	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	B	B	B	A	C
18	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	B	B	B	A	B
19	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	B	A	B	A	B

#	Name	EphB4 IC_{50}	EphA2 IC_{50}	KDR IC_{50}	Flt-1 IC_{50}	EGFR IC_{50}	ErbB2 IC_{50}
20	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	B	B	A	B	A	B
21	N-(3,4-dichlorophenyl)-7-{[(3R,8aR)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	B	A	B	A	B
22	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	B
23	N-(3,4-dichlorophenyl)-7-{[(3S,8aR)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	A
24	N-(3,4-dichlorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	B
25	N-(3,4-dichlorophenyl)-7-{[(3R,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	A
26	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	B
27	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	A	A	B
28	N-(3-chloro-2,4-difluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	B	B	A	B
29	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	B

#	Name	EphB4 IC_{50}	EphA2 IC_{50}	KDR IC_{50}	Flt-1 IC_{50}	EGFR IC_{50}	ErbB2 IC_{50}
30	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine	A	A	A	B	A	B
31	1,4:3,6-dianhydro-5-({[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol	B	B	B	C	A	B
32	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-glucitol	B	C	B	C	A	B
33	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-xylo-hexitol	A	B	B	C	A	B
34	1,4:3,6-dianhydro-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol	A	B	B	C	A	B
35	1,4:3,6-dianhydro-5-({[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol	A	B	C	C	A	B
36	1,4:3,6-dianhydro-5-({[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-glucitol	A	C	B	C	A	C
37	1,4:3,6-dianhydro-2-deoxy-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-O-methyl-D-threo-hexitol	B	B	B	C	A	C
38	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-glucitol	B	B	B	C	A	B
39	(3S,9aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one	A	A	A	B	A	C

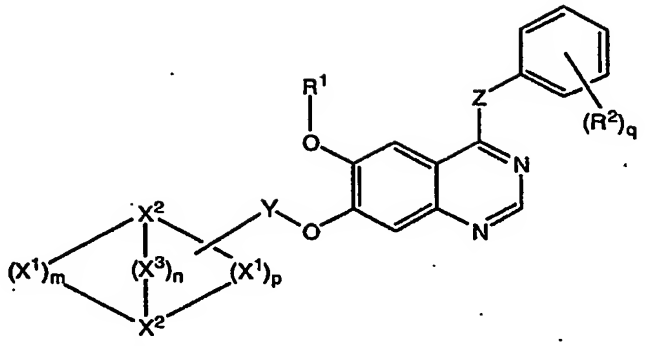
#	Name	EphB4 IC_{50}	EphA2 IC_{50}	KDR IC_{50}	Flt-1 IC_{50}	EGFR IC_{50}	ErbB2 IC_{50}
40	(3S,9aR)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one	A	B	B	B	A	C
41	(3S,8aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one	A	B	A	B	A	B
42	(3S,8aR)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one	A	A	A	B	A	C
43	(3S,8aS)-3-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one	A	B	A	B	A	C
44	(3S,8aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one	A	B	B	B	A	C
45	N-(3,4-dichlorophenyl)-7-({2-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]ethyl}oxy)-6-(methyloxy)quinazolin-4-amine	A	B	A	B	A	A
46	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(8aR)-tetrahydro-1H-[1,3]thiazolo[4,3-c][1,4]oxazin-6-ylmethyl]oxy}quinazolin-4-amine	A	B	B	B	A	B
47	N-(3,4-dichlorophenyl)-7-{[2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ethyl]oxy}-6-(methyloxy)quinazolin-4-amine	B	B	B	C	A	A
48	N-(3,4-dichlorophenyl)-7-{[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine	B	B	B	C	A	B
49	N-(3,4-dichlorophenyl)-7-{[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]oxy}-6-(methyloxy)quinazolin-4-amine	B	B	B	C	A	B

#	Name	EphB4 IC_{50}	EphA2 IC_{50}	KDR IC_{50}	Flt-1 IC_{50}	EGFR IC_{50}	ErbB2 IC_{50}
50	N-(3,4-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-6-(methyloxy)quinazolin-4-amine	C	C	C	C	A	C
51	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	B	C	C	C	A	C
52	1,4:3,6-dianhydro-2-O-[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	A	C	C	C	A	B
53	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	B	C	B	C	A	B
54	1,4:3,6-dianhydro-2-O-methyl-5-O-{6-(methyloxy)-4-[(2,3,4-trichlorophenyl)amino]quinazolin-7-yl}-L-iditol	B	C	C	C	A	C
55	1,4:3,6-dianhydro-5-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-D-xylo-hexitol	B		B	C	A	B
56	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	B	C	C	C	A	B
57	dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-sorbose ethylene glycol acetal	B	C	C	C	A	B
58	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	B	C	C	C	A	C
59	1,4:3,6-dianhydro-2-O-[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	B	C	C	C	A	C

#	Name	EphB4 IC_{50}	EphA2 IC_{50}	KDR IC_{50}	Flt-1 IC_{50}	EGFR IC_{50}	ErbB2 IC_{50}
60	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-(difluoromethyl)-L-iditol	B	C	C	B	A	B
61	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	B	C	C	C	A	B
62	1,4:3,6-dianhydro-2-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	B	C	C	C	A	B
63	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	B	C	C	D	A	B
64	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-ethyl-L-iditol	B	C	C	B	A	B
65	1,4:3,6-dianhydro-2-O-[4-[(3-bromo-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	C	C	D	D	A	C
66	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol	C	C	D	D	A	C
67	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-D-xylo-hexitol	C	C	C	C	A	B
68	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-D-glucitol	C	C	C	C	A	C

What is claimed is:

1. A compound of Formula **I**,



I

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

R^1 is an optionally substituted lower alkyl;

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^4$, $-C(O)R^3$, and optionally substituted lower alkyl;

R^3 is -H or R^4;

R^4 is selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, and optionally substituted lower heterocyclylalkyl; or

R^3 and R^4, when taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl ring, said optionally substituted five- to seven-membered heterocyclyl ring optionally containing at least one additional heteroatom selected from N, O, S, and P;

q is 0 to 5;

Z is selected from $-OCH_2-$, -O-, $-S(O)_{0-2}-$, $-N(R^5)CH_2-$, and $-NR^5-$;

R^5 is -H or optionally substituted lower alkyl;

X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system containing up to four heteroatoms represented by any of X^1, X^2, and X^3;

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted lower alkylene linker, between the oxygen at the 7-position of the quinazoline ring system of I and either 1) any ring atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between any heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7, and the oxygen at the 7-position of the quinazoline ring system of I;

or Y is absent, when Y is absent, said saturated bridged ring system, via a carbon atom thereof, is directly attached to the oxygen at the 7-position of the quinazoline ring system of I;

m and p are each independently 1-4;

n is 0-2, when n = 0, then there is a direct bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^4$, $-S(O)_{0-2}R^4$, $-SO_2NR^3R^4$, $-CO_2R^3$, $-C(O)NR^3R^4$, $-N(R^3)SO_2R^4$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted lower heterocyclylalkyl, and an attachment point for either Y or the oxygen at the 7-position of the quinazoline ring system of I; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclic ring, said optionally substituted

three- to seven-membered spirocyclic ring optionally containing at least one additional heteroatom selected from N, O, S, and P; and

R^8 is selected from R^3, Y, $-SO_2NR^3R^4$, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$;

with the proviso that when Y is a C_{1-6} alkylene, Z is -NH- or $-N(CH_3)-$, R^1 is a C_{1-6}alkyl optionally substituted in the 2-position by -OH or a C_{1-4}alkoxy group, R^2 is -H or halogen, n = 0, and the atoms, X^1, of one bridge of the saturated bridged ring system, when combined with both bridgehead atoms, X^2, of the saturated bridged ring system, represent:

either a pyrrolidine ring or a piperidine ring, and any atom, X^1 or X^2, of either of said pyrrolidine ring or said piperidine ring is attached to Y, then the other bridge of said saturated bridged ring system cannot be any one of $-OC(O)CH_2-$, $-CH_2OC(O)-$, $-OC(O)CH_2CH_2-$, $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, $-OC(O)CH_2NH-$, $-OC(O)CH_2N(C_{1-4}alkyl)-$, and $-OC(O)CH_2O-$; or

either a piperazine ring or a 4-(C_{1-4}alkyl)-piperazine ring, and any atom, X^1 or X^2, of either of said piperazine ring or said 4-(C_{1-4}alkyl)-piperazine ring is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 2- and the 3-position of either of said piperazine ring or said 4-(C_{1-4}alkyl)-piperazine ring, cannot be one of $-CH_2OC(O)CH_2-$, $-CH_2CH_2OC(O)-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups; or

a piperazine ring, and any atom, X^1 or X^2, of said piperazine ring is attached to Y, then the other bridge of said saturated bridged ring system, only when attached via the 3- and the 4-position of said piperazine ring, cannot be one of $-C(O)OCH_2CH_2-$, $-CH_2OC(O)CH_2-$, and either of the two aforementioned bridges optionally substituted by one or two C_{1-2}alkyl groups, and only when either of the two aforementioned bridges are attached to the 3-position of said piperazine ring via their left-hand end as depicted above; or

a 2-oxomorpholine ring, said 2-oxomorpholine ring attached to Y via its 4-position, then the other bridge of said saturated bridged ring system, only

when attached via the 5- and the 6-position of said 2-oxomorpholine ring, cannot be one of $-(CH_2)_g-$, $-CH_2WCH_2-$, $-CH_2WCH_2CH_2-$, and $-CH_2CH_2WCH_2-$, wherein W is -O-, $-S(O)_{0-2}-$, -NH-, or $-N(C_{1-4}alkyl)-$ wherein g is 2, 3, or 4.

2. The compound according to claim 1, wherein Z is $-NR^5-$.

3. The compound according to claim 2,wherein R^2 is halogen.

4. The compound according to claim 3, wherein R^1 is an unsubstituted lower alkyl.

5. The compound according to claim 4, wherein the saturated bridged ring system has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], [3.1.0], [3.3.3], [3.3.2], [3.3.1], [3.2.2], [3.2.1], [2.2.2], and [2.2.1].

6. The compound according to claim 5, wherein Y is selected from $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, $-CH_2-$, and absent.

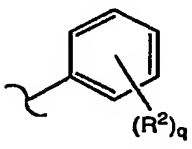
7. The compound according to claim 6, wherein n = 0 and the saturated bridged ring system has a geometry selected from the group consisting of [4.4.0], [4.3.0], [4.2.0], [4.1.0], [3.3.0], [3.2.0], and [3.1.0].

8. The compound according to claim 7, wherein Y is either $-CH_2-$ or absent.

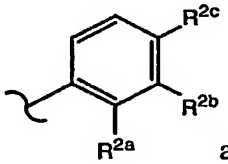
9. The compound according to claim 8, wherein said saturated bridged ring system contains only one ring heteroatom, and said only one ring heteroatom is either $-NR^8-$, when X^1, or a bridgehead nitrogen, when X^2.

10. The compound according to claim 9, wherein q = 3.

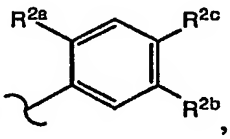
11. The compound according to claim 10, wherein



of **I** is selected from:



and



, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

12. The compound according to claim 11, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

13. The compound according to claim 12, wherein R^5 is -H.

14. The compound according to claim 13, wherein R^1 is methyl.

15. The compound according to claim 14, wherein said only one ring heteroatom is $-NR^8-$, and wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

16. The compound according to claim 15, wherein the remainder of atoms, X^1 and X^2, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are -H, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

17. The compound according to claim 14, wherein said only one ring heteroatom is a bridgehead nitrogen, wherein the remainder of atoms, X^1 and X^2, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are either -H or unsubstituted lower alkyl, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

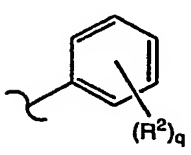
18. The compound according to claim 6, wherein n = 1 and the saturated bridged ring system has a geometry selected from the group consisting of [3.3.1], [3.2.1], and [2.2.1].

19. The compound according to claim 18, wherein Y is either $-CH_2-$ or absent.

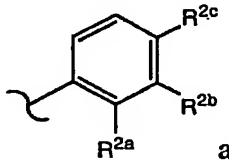
20. The compound according to claim 19, wherein said saturated bridged ring system contains only one ring heteroatom, and said only one ring heteroatom is either $-NR^8-$, when X^1 or X^3, or a bridgehead nitrogen, when X^2.

21. The compound according to claim 20, wherein q = 3.

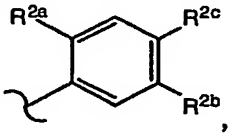
22. The compound according to claim 21, wherein



of **I** is selected from:



and



, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

23. The compound according to claim 22, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

24. The compound according to claim 23, wherein R^5 is -H.

25. The compound according to claim 24, wherein R^1 is methyl.

26. The compound according to claim 25, wherein said only one ring heteroatom is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

27. The compound according to claim 26, wherein the remainder of atoms, X^1, X^2, and X^3, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are -H, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

28. The compound according to claim 25, wherein said only one ring heteroatom is a bridgehead nitrogen, wherein the remainder of atoms, X^1, X^2, and X^3, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are either -H or unsubstituted lower alkyl, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of **I**.

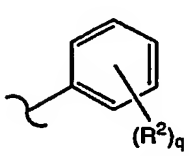
29. The compound according to claim 6, wherein n = 2 and the saturated bridged ring system has a geometry selected from the group consisting of [3.3.2], [3.2.2], and [2.2.2].

30. The compound according to claim 29, wherein Y is either $-CH_2-$ or absent.

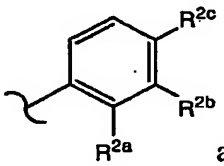
31. The compound according to claim 30, wherein said saturated bridged ring system contains only one ring heteroatom, and said only one ring heteroatom is either $-NR^8-$, when X^1 or X^3, or a bridgehead nitrogen, when X^2.

32. The compound according to claim 31, wherein q = 3.

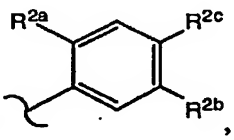
33. The compound according to claim 32, wherein



of **I** is selected from:



and



, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

34. The compound according to claim 33, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

35. The compound according to claim 34, wherein R^5 is -H.

36. The compound according to claim 35, wherein R^1 is methyl.

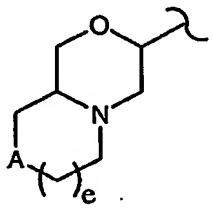
37. The compound according to claim 36, wherein said only one ring heteroatom is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

38. The compound according to claim 37, wherein the remainder of atoms, X^1, X^2, and X^3, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are -H, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of I.

39. The compound according to claim 35, wherein said only one ring heteroatom is a bridgehead nitrogen, wherein the remainder of atoms, X^1, X^2, and X^3, in said saturated bridged ring system are $-C(R^6)R^7-$, wherein R^6 and R^7 are either -H or unsubstituted lower alkyl, except that one of R^6 and R^7, for only one ring atom of said saturated bridged ring system, must be Y or a direct bond to the oxygen at the 7-position of the quinazoline ring system of I.

40. The compound according to claim 6, wherein Y is selected from $-CH_2CH_2CH_2-$, $-CH_2CH_2-$, and $-CH_2-$.

41. The compound according to claim 40, wherein said saturated bridged ring system is of formula II



II

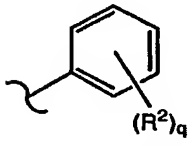
wherein A is selected from $-O-$, $-S(O)_{0-2}-$, $-NR^8-$, and absent, and e is 0 or 1.

42. The compound according to claim 41, wherein Y is $-CH_2-$ and e is 1.

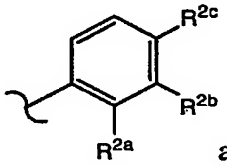
43. The compound according to claim 42, wherein A is $-NR^8-$, wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

44. The compound according to claim 43, wherein q = 3.

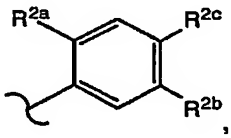
45. The compound according to claim 44, wherein



of I is selected from:



and



, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

46. The compound according to claim 45, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

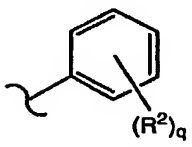
47. The compound according to claim 46, wherein R^5 is -H.

48. The compound according to claim 47, wherein R^1 is methyl.

49. The compound according to claim 42, wherein A is -O-.

50. The compound according to claim 49, wherein q = 3.

51. The compound according to claim 50, wherein



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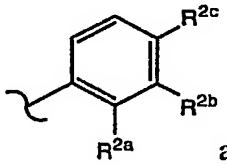

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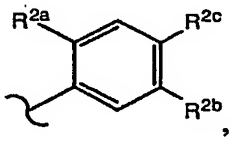


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

52. The compound according to claim 51, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

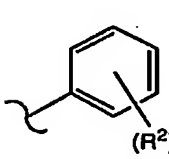
53. The compound according to claim 52, wherein R^5 is -H.

54. The compound according to claim 53, wherein R^1 is methyl.

55. The compound according to claim 42, wherein A is absent.

56. The compound according to claim 55, wherein q = 3.

57. The compound according to claim 56, wherein



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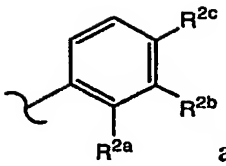

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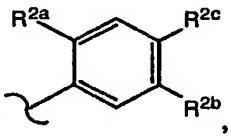


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

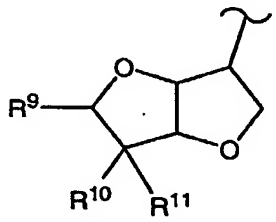
58. The compound according to claim 57, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

59. The compound according to claim 58, wherein R^5 is -H.

60. The compound according to claim 59, wherein R^1 is methyl.

61. The compound according to claim 6, wherein Y is selected from $-CH_2CH_2-$, $-CH_2-$, and absent.

62. The compound according to claim 61, wherein said saturated bridged ring system is of formula **III**



III

wherein R^9, R^{10}, and R^{11} are each independently selected from -H, and $-OR^{12}$; or

R^9 is selected from -H, and $-OR^{12}$, and R^{10} and R^{11}, when taken together, are either an optionally substituted alkylidene or an oxo;

R^{12} is selected from -H, $-C(O)R^4$, optionally substituted lower alkylidyne, optionally substituted lower arylalkylidyne, optionally substituted lower heterocyclylalkylidyne, optionally substituted lower alkylidene, optionally substituted lower alkylidenearyl, optionally substituted lower alkylideneheterocyclyl, optionally substituted lower alkyl, optionally substituted lower alkylaryl, optionally substituted aryl, optionally substituted lower heterocyclylalkyl, and optionally substituted heterocyclyl;

or two R^{12}'s, when taken together, form 1) a corresponding spirocyclic ketal when said two R^{12}'s stem from R^{10} and R^{11}, or 2) a corresponding cyclic ketal when said two R^{12}'s stem from R^9 and one of R^{10} and R^{11}.

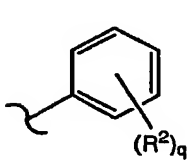
63. The compound according to claim 62, wherein one of R^{10} and R^{11} is $-OR^{12}$, wherein R^{12} is selected from -H, $-C(O)R^4$, and optionally substituted lower alkyl; and R^9 and the other of R^{10} and R^{11} are both -H.

64. The compound according to claim 63, wherein Y is either $-CH_2-$ or absent.

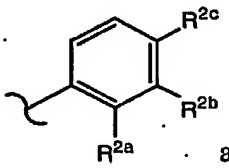
65. The compound according to claim 63, wherein R^9 is an alkyl group containing at least one fluorine substitution thereon.

66. The compound according to claim 64, wherein q = 3.

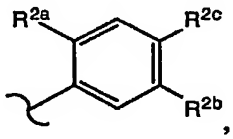
67. The compound according to claim 66, wherein



of **I** is selected from:



and



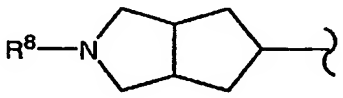
, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

68. The compound according to claim 67, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

69. The compound according to claim 68, wherein R^5 is -H.

70. The compound according to claim 69, wherein R^1 is methyl.

71. The compound according to claim 61, wherein said saturated bridged ring system is of formula **IV**



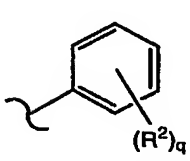
IV

wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

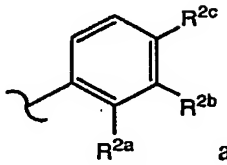
72. The compound according to claim 71, wherein Y is either $-CH_2-$ or absent.

73. The compound according to claim 72, wherein q = 3.

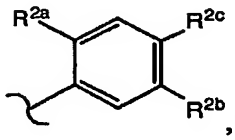
74. The compound according to claim 73, wherein



of **I** is selected from:



and



, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

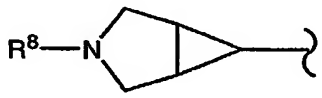
75. The compound according to claim 74, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

76. The compound according to claim 75, wherein R^5 is -H.

77. The compound according to claim 76, wherein R^1 is methyl.

78. The compound according to claim 77, wherein R^8 is methyl.

79. The compound according to claim 61, wherein said saturated bridged ring system is of formula **V**



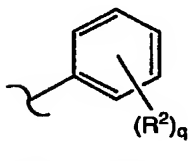
V

wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

80. The compound according to claim 79, wherein Y is $-CH_2-$.

81. The compound according to claim 80, wherein q = 3.

82. The compound according to claim 81, wherein



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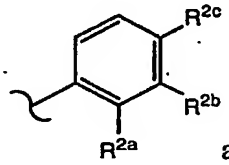

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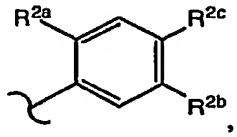


, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

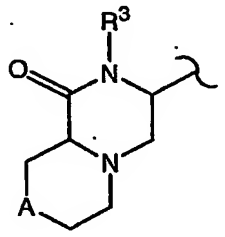
83. The compound according to claim 82, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

84. The compound according to claim 83, wherein R^5 is -H.

85. The compound according to claim 84, wherein R^1 is methyl.

86. The compound according to claim 85, wherein R^8 is methyl.

87. The compound according to claim 61, wherein said saturated bridged ring system is of formula **VI**



VI

wherein A is selected from -O-, -S(O)$_{0-2}$-, -NR^8-, -CR^{6}R^7-, and absent.

88. The compound according to claim 87, wherein R^3 is selected from -H and optionally substituted alkyl.

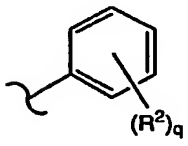
89. The compound according to claim 88, wherein A is either -CR^{6}R^7- or absent.

90. The compound according to claim 89, wherein A is either -CH_2- or absent.

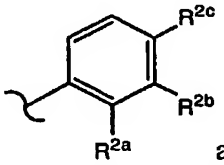
91. The compound according to claim 90, wherein Y is -CH_2-.

92. The compound according to claim 91, wherein q = 3.

93. The compound according to claim 92, wherein



of **I** is selected from:



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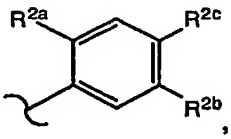


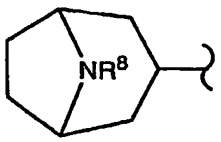
, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

94. The compound according to claim 93, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

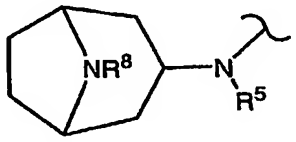
95. The compound according to claim 94, wherein R^5 is -H.

96. The compound according to claim 95, wherein R^1 is methyl.

97. The compound according to claim 61, wherein Y is $-CH_2CH_2-$ and The compound according to claim 61, wherein said saturated bridged ring system is chosen from either of formula **VII** or **VIII**



VII

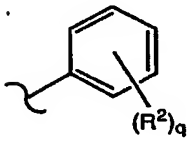


VIII

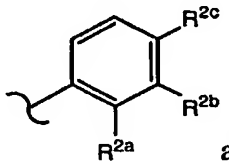
wherein R^8 is selected from -H, optionally substituted lower alkyl, $-CO_2R^4$, $-C(O)NR^3R^4$, $-SO_2R^4$, and $-C(O)R^3$.

98. The compound according to claim 97, wherein q = 3.

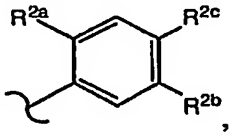
99. The compound according to claim 98, wherein



of **I** is selected from:



and



, wherein R^{2a}, R^{2b}, and R^{2c} are each independently selected from F, Cl, and Br.

100. The compound according to claim 99, wherein R^{2a} is F, R^{2b} is Cl, and R^{2c} is either Cl or Br.

101. The compound according to claim 100, wherein R^5 is -H.

102. The compound according to claim 101, wherein R^1 is methyl.

103. The compound according to claim 102, wherein R^8 is methyl.

104. The compound according to claim 1, selected from the compounds in the following table:

#	Name
1	N-(3,4-dichloro-2-fluorophenyl)-7-({[(3aR,5r,6aS)-2-(1-methylethyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
2	N-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3aR,5r,6aS)-2-(1-methylethyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine

#	Name
3	7-({[(3aR,5r,6aS)-2-acetyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-N-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)quinazolin-4-amine
4	N-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3aR,5r,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine
5	ethyl (3aR,6aS)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate
6	N-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3aR,5r,6aS)-2-(methylsulfonyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
7	N-(3,4-dichloro-2-fluorophenyl)-7-({[(3aR,5r,6aS)-2-ethyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
8	N-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3aR,5r,6aS)-2-(2-methylpropyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
9	N-(3,4-dichloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
10	N-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
11	N-(3-chloro-2,4-difluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
12	N-(4,5-dichloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
13	N-(4-bromo-5-chloro-2-fluorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
14	N-(4-bromo-2,3-dichlorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
15	N-(3,4-dichlorophenyl)-7-({[(3aR,5s,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
16	N-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3aR,5r,6aS)-2-ethyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
17	N-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3aR,5r,6aS)-2-(2-methylpropyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
18	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine

#	Name
19	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
20	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
21	N-(3-chloro-2,4-difluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
22	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
23	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
24	N-(3-chloro-2,4-difluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
25	N-(3,4-dichlorophenyl)-7-[(hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl)oxy]-6-(methyloxy)quinazolin-4-amine
26	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
27	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
28	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3S,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
29	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
30	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3R,9aS)-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
31	N-(3,4-dichlorophenyl)-7-{[(3R,8aR)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
32	N-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
33	N-(3,4-dichlorophenyl)-7-{[(3S,8aR)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
34	N-(3,4-dichlorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine

#	Name
35	N-(3,4-dichlorophenyl)-7-{[(3R,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
36	N-(3,4-dichloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
37	N-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
38	N-(3-chloro-2,4-difluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
39	N-(4-bromo-2,3-dichlorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
40	N-(4,5-dichloro-2-fluorophenyl)-7-{[(3S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
41	1,4:3,6-dianhydro-5-({[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
42	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-glucitol
43	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-xylo-hexitol
44	1,4:3,6-dianhydro-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
45	1,4:3,6-dianhydro-5-({[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
46	1,4:3,6-dianhydro-5-({[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-glucitol
47	1,4:3,6-dianhydro-2-deoxy-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-O-methyl-D-threo-hexitol
48	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-glucitol
49	(3S,9aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one
50	(3S,9aR)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one

#	Name
51	(3S,8aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one
52	(3S,8aR)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one
53	(3S,8aS)-3-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one
54	(3S,8aS)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2H)-one
55	N-(3,4-dichlorophenyl)-7-({2-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]ethyl}oxy)-6-(methyloxy)quinazolin-4-amine
56	N-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(8aR)-tetrahydro-1H-[1,3]thiazolo[4,3-c][1,4]oxazin-6-ylmethyl]oxy}quinazolin-4-amine
57	N-(3,4-dichlorophenyl)-7-{[2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ethyl]oxy}-6-(methyloxy)quinazolin-4-amine
58	N-(3,4-dichlorophenyl)-7-{[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
59	N-(3,4-dichlorophenyl)-7-{[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]oxy}-6-(methyloxy)quinazolin-4-amine
60	N-(3,4-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-6-(methyloxy)quinazolin-4-amine
61	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
62	1,4:3,6-dianhydro-2-O-[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
63	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
64	1,4:3,6-dianhydro-2-O-methyl-5-O-{6-(methyloxy)-4-[(2,3,4-trichlorophenyl)amino]quinazolin-7-yl}-L-iditol
65	1,4:3,6-dianhydro-5-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-D-xylo-hexitol
66	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol

#	Name
67	dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-sorbose ethylene glycol acetal
68	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
69	1,4:3,6-dianhydro-2-O-[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
70	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-(difluoromethyl)-L-iditol
71	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
72	1,4:3,6-dianhydro-2-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
73	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
74	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-ethyl-L-iditol
75	1,4:3,6-dianhydro-2-O-[4-[(3-bromo-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
76	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
77	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-D-xylo-hexitol
78	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-D-glucitol
79	methyl 3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-alpha-L-idofuranoside
80	3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-1,2-O-(1-methylethylidene)-beta-L-xylo-hexofuranose
81	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-5-methylidene-D-xylo-hexitol
82	methyl 3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-beta-L-idofuranoside

#	Name
83	N-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-[(octahydro-2H-quinolizin-3-ylmethyl)oxy]quinazolin-4-amine

105. A pharmaceutical composition comprising a compound according to any one of claims 1-104 and a pharmaceutically acceptable carrier.

106. A method of treating cancer and diseases related to angiogenesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition according to claim 105.

107. A method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of a composition according to claim 105.

108. The method according to claim 107, wherein the kinase is selected from a family of ephrin receptor tyrosine kinases.

109. The method of claim 107, wherein modulating the *in vivo* activity of the kinase comprises inhibition of said kinase.

110. The method of claim 108, wherein the family of ephrin receptor tyrosine kinases comprises EphA2 and EphB4.

ABSTRACT

The present invention provides compounds for modulating ephrin receptor kinase activity and methods of treating diseases mediated by ephrin activity utilizing the compounds and pharmaceutical compositions thereof. Diseases mediated by ephrin activity include, but are not limited to, diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth. Compounds of the invention include "spectrum selective" kinase modulators, compounds that inhibit, regulate and/or modulate signal transduction across subfamilies of receptor-type tyrosine kinases including those of the ephrin receptor tyrosine kinase subfamily.